

AMERICAN JOURNAL

OF

OBSTETRICS AND GYNECOLOGY

ADVISORY EDITORIAL BOARD

FRED L. ADAIR
BROOKE M. ANSPACH
JAMES R. BLOSS
LUCIUS E. BURCH
WALTER W. CHIPMAN
WILLARD R. COOKE
HARRY S. CROSSEN
THOMAS S. CULLEN
ARTHUR H. CURTIS
WILLIAM C. DANFORTH
WALTER T. DANNREUTHER
CARL H. DAVIS
JOSEPH B. DELEE
ROBERT L. DICKINSON

PALMER FINDLEY
C. FREDERIC FLUHMANN
ROBERT T. FRANK
JOHN R. FRASER
WILLIAM P. HEALY
F. C. IRVING
JENNINGS C. LITZENBERG
FRANK W. LYNCH
JAMES C. MASSON
JAMES R. MCCORD
NORMAN F. MILLER
CHARLES C. NORRIS
EMIL NOVAK
EVERETT D. PLASS

ISIDOR C. RUBIN
JOHN A. SAMPSON
OTTO H. SCHWARZ
H. J. STANDER
FRED J. TAUSSIG
PAUL TITUS
NORRIS W. VAUX
WILLIAM H. VOGT
GEORGE GRAY WARD
RAYMOND E. WATKINS
BENJAMIN P. WATSON
PHILIP F. WILLIAMS
KARL M. WILSON

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY; THE AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS, AND ABDOMINAL SURGEONS; NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA; BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY; NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY; BALTIMORE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRIC SOCIETY; CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY; WASHINGTON GYNECOLOGICAL SOCIETY; PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY; OBSTETRICAL SOCIETY OF BOSTON; LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; SOUTH ATLANTIC ASSOCIATION OF OBSTETRICS AND GYNECOLOGY

EDITORS

GEORGE W. KOSMAK HUGO EHRENFEST

ASSOCIATE EDITORS

HOWARD C. TAYLOR, JR. . . . WILLIAM J. DIECKMANN

VOLUME 40

JULY—DECEMBER, 1940

ST. LOUIS

THE C. V. MOSBY COMPANY

1940

COPYRIGHT, 1940, BY THE C. V. MOSBY COMPANY

(All rights reserved)

*Printed in the
United States of America*

*Press of
The C. V. Mosby Company
St. Louis*

American Journal of Obstetrics and Gynecology

VOL. 40

JULY, 1940

No. 1

Original Communications

NUTRITION STUDY IN PREGNANCY*

CORRELATION BETWEEN DIETARY SURVEY OF VITAMIN A CONTENT AND DARK ADAPTATION TIME

PHILIP F. WILLIAMS, M.D., BERNARD HARK, M.D., AND
FLORENCE G. FRALIN, B.S., PHILADELPHIA, PA.

(From the Prenatal Clinics of the Presbyterian and Jewish Hospitals)

THIS report presents the results of an estimation of the vitamin A content in the diets of 123 pregnant women, a determination of their dark adaptation time by the adaptometer, a study of the effect upon the deficiencies following administration of vitamin A concentrate, and a correlation of the findings with several obstetric factors.

Vitamin A, an essential food factor, is metabolized in the human body from its precursors, which, in turn, are metabolic products of plants. It is one of an increasing group of organic substances regarded as indispensable for growth and maintenance of normal structure and function of body tissue. It is said to be intimately concerned with the reproductive processes of experimental and domestic animals. This vitamin in its most nearly pure naturally occurring form is found in fish liver oils. In the human body, carotene, its precursor or provitamin, is converted to vitamin A in the liver. Carotene is contained in the yellow or green colored matter of many vegetables and fruits.

Eggs, milk, and some milk products, and liver are the most important vitamin A food sources of animal origin. The best plant sources are the green or yellow fruits and vegetables.

*This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.

Read by invitation at the Third Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists at Richmond, Virginia, February 9, 1940.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

The vitamin A activity of milk and eggs is derived from the plant material consumed by the cow and the hen; and milk becomes a very important source of vitamin A supply when one considers that it is consumed in fairly large quantities.

Animal liver contains a high concentration of vitamin A (approximately 2,780 Sherman units per ounce of beef liver); it is the site of transformation of carotene into actual vitamin A, and surplus vitamin A is stored there. But, "increased appreciation of, and consumer demand for, liver cannot be met by increased production of liver as an independent food crop."^{*}

Thin green leaves are among the best sources of vitamin A. There seems to be a parallel between chlorophyll content and vitamin A activity, but the exact relationship has not yet been established. The yellow color of the carotene may be an index of the vitamin A activity in many plant products, as for example, carrots and sweet potatoes, two valuable vegetable sources, and apricots, yellow peaches and bananas, very good fruit sources.¹

Vitamin A is essential to normal nutrition at all ages. One of the early symptoms of deficiency is hemeralopia, poor visual adaptation to semidarkness. Mild deficiency symptoms reported include retarded growth, possible lowered resistance to infection, particularly in the upper respiratory tract, lack of vigor and appetite, decreased reproduction and lactation, dry skin and poor teeth. More serious deficiencies reported include such symptoms as xerophthalmia, lowered resistance to infections entering mucous surfaces, sterility, loss of weight, calculus formation in kidney and bladder, and a weakening and metaplasia of epithelial tissues.

The requirements for the human being have been worked out from various aspects and are usually expressed in terms of international units per kilogram of body weight. Quantitatively, according to Guilbert and Hart,² the requirement for vitamin A is strikingly small; six to eight micrograms daily per kilogram of body weight are necessary for cattle, sheep, and swine.

Since the symptom of partial night blindness lends itself to physical measurement, several investigators have made observations on the amounts of vitamin A necessary to prevent it. They based their conclusions on the ability of their subjects to discern differences in brightness of illumination.

After studying two matched groups of young male adults, Edmund and Clemesen³ concluded that 20 to 22 international units of vitamin A value per kilogram of body weight should prevent visual dysadaptation. An average of 40 international units per kilogram maintained an optimal visual response without providing body storage in the series studied by Booher, Collison, and Hewston.⁴

Stiebelling and Phipard⁵ conclude from the Booher study that the average American diet should provide an average of 60 international units per kilogram to cover average minimum requirements for maintaining optimal visual response. They suggest that to obtain a storage reserve and to provide for the needs of those with higher requirements it would appear practicable to establish a 50 per cent margin

^{*}Sherman: *Chemistry of Foods and Nutrition*, New York, 1937, The Macmillan Company.

of safety as an aim in ideal dietary plans. For a 70 kilogram man this would amount to at least 6,000 international units of vitamin A value per day. Six to eight thousand units of vitamin A value can be furnished by ordinary food if great care is taken in its selection.

Several observers⁶⁻⁸ have noted that only minute traces of vitamin A and carotene are found in the serum of blood from the umbilical cord of human infants. Others have noted that the fetal liver contains only 14 to 17 units per gram as against an average content in the adult liver of 220 units per gram. Dann⁹ found that in spite of the apparent necessity of vitamin A for fetal growth it was impossible to raise the vitamin content of the livers of fetal rats by administering either vitamin A or carotene in large doses to the pregnant mothers. By administering enormous doses of vitamin A to the pregnant rabbit, a slight relative increase in the storage of vitamin A in the fetal liver was accomplished. The deleterious effects upon the reproductive process in dairy animals, swine, and experimental animals of a diet deficient in vitamin A values have been established.

Sure¹⁰ and Mason¹¹ have shown that a lack of vitamin A in the diets of rats upset the estrous cycle, and caused resorption of the fetus; if a litter was born, the young were immature and showed signs of incipient xerophthalmia. Cattle in California, deprived of green food during a dry season, had stillborn calves whose livers showed no vitamin A. Those calves born alive succumbed readily to infections. Here estrus also failed to return.¹²

These effects of a vitamin A deficiency accentuate the importance for an optimum amount of this food factor in the diet during pregnancy. Among other basic reasons for such an increase may be mentioned the increased metabolism of the pregnant woman, the very active metabolic processes of the fetus in relation to its weight, and the need for an increased storage in the woman's body to provide for the demands of lactation. The surprising difference between content of vitamin A in the fetal liver and the adult liver, and the fact that but minute traces of either vitamin A or carotene are found in the umbilical cord blood serum suggest that the placenta prevents the passage of any marked quantity of vitamin A to the fetus and its structures. This is in contrast to the finding of an increased amount of vitamin C in the cord blood of the fetus as compared with a simultaneous maternal blood content. To us the question is not answered as to the reason for such a small amount of such an essential growth factor as vitamin A in the fetal blood and the tissues. If the fetus has the same comparative need for vitamin A in its metabolic oxidative processes, in what form is it transmitted from the mother?

The newborn child requires 2,000 units of vitamin A a day¹³ for its growth and for the liver storage which increases rapidly in the early weeks of life. Such need increases with the growth of the child. This necessitates a maternal storage during pregnancy as well as a continuance of optimum requirements during lactation.

The argument that excess storage does take place during pregnancy can be somewhat strengthened by the discovery in the literature that maternal storage is more than double that of ordinary human storage.

Busson¹⁴ analyzed for vitamin A the liver of one woman who died in shock shortly after cesarean section, and has reported the determination of 462 Lovibond Blue Units in 0.5 Gm. of liver. Although its validity might be questioned, applying Moore's¹⁵ conversion formula, $1 \text{ B.U.} \times 0.6 = 1 \text{ international unit}$, the liver of this patient contained 544.4 international units of vitamin A per gram, as contrasted with 220 international units per gram of normal human adult liver.

The increased requirements of pregnancy and lactation probably are met by doubling the adult's usual requirements per unit of body weight. For a 132 pound, 60 kilogram, pregnant woman, then, at double the usual 60 unit value for minimum requirement, the daily requirement would be 7,200 international units of vitamin A value. The Technical Commission of the League of Nations¹⁶ recommends 9,000 international units of vitamin A for the pregnant and lactating woman.

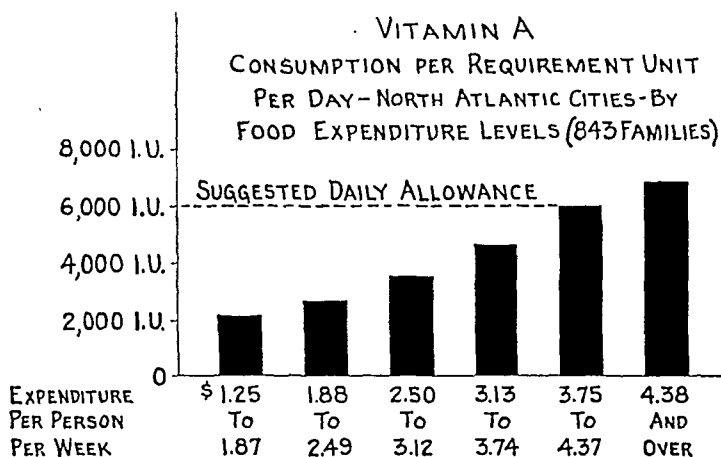


Fig. 1.—Vitamin A consumption per requirement unit per day, North Atlantic cities, by food expenditure levels (843 families). (From Stiebeling and Phipard.⁵)

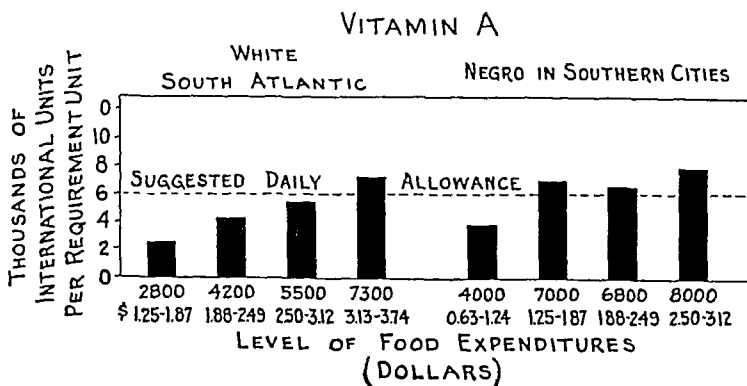


Fig. 2.—Vitamin A consumption per requirement unit per day. White in South Atlantic cities and Negro in Southern cities, by food expenditure levels. (Adapted from Stiebeling and Phipard.)

Dr. Maurice B. Strauss in a personal communication says, "I feel that it is wise to hold out for high levels, particularly in view of the many metabolic and gastrointestinal changes which occur in pregnancy and which probably alter the absorption, utilization and requirement of nutritional factors."

In their recent estimate of the adequacy of diets of different population groups, Stiebeling and Phipard investigated, among other food factors, the content of vitamin A. They found that values as high as their suggested daily allowance scale for the requirement unit of an adult male, twenty years or over, of 6,000 international units were obtained in groups of families living in Southern cities, even when their expenditures for food were as little as \$0.63 to \$1.24 a person per week. In their dietary survey of the families of employed workers in eight major geographical centers of the United States, the authors brought to light many surpris-

ing facts regarding the distribution of dietary vitamin A values. It is of interest at this meeting to compare the North Atlantic cities, which include Philadelphia, the South Atlantic cities, and the negro of the Southern cities, for the average values for vitamin A in their diets at various economic levels.

In the North Atlantic cities, according to Stiebeling and Phipard (Fig. 1), at a food expenditure level of \$1.25 to \$1.87 a person a week, the average vitamin A value of the diets of the families investigated was 2,100 international units a requirement unit a day. Almost 70 per cent of the diets furnished less than 2,000 units, whereas the top 13 per cent furnished more than 4,000 units per requirement unit a day. Even when the expenditure reached \$2.50 to \$3.12 a person a week, as many as 29 per cent of the families in the North Atlantic cities obtained fewer than 2,000 units a requirement unit a day. In the South Atlantic cities with an expenditure of \$1.25 to \$1.87 (Fig. 2), the average value reached 2,800 units, a 25 per cent increase over the North Atlantic area. At the same financial output, the negro in the Southern cities obtained 6,600 units. At \$3.13 to \$3.74 per person per week for food the South Atlantic average of 7,300 units goes over the required allowance for the first time. The North Atlantic average still trails at 4,200 units, and only approximates the requirement allowance, with 5,900 units, at an expenditure of \$3.75 to \$4.37 per person per week for food.

Although the cost is unknown it may be interesting at this point to mention the pellagra-producing diet published by Ross and his co-workers¹⁷ in their investigation of the relation of dietary factors to pregnancy toxemia (Table I). It is to be presumed, from the context of their report, that many pregnant women in the South subsist on a diet similar to one which the values show is markedly deficient in vitamin A.

TABLE I. VITAMIN A VALUE IN A PELLAGRA-PRODUCING DIET
(AS REPORTED BY ROSS)

FOOD	QUANTITY (GM.)	VITAMIN A VALUE INT. UNITS
Cornmeal (yellow)	92	770
Cane syrup	105	0
Flour	111	0
Lard	81	0
Rice	25	0
Field peas	90	500-3,000*
Hominy grits	51	0
Fat salt pork	60	300
Total value		1,570-4,070

*Values by different assays.

Consequently, it is evident that in both the North and South Atlantic cities, though to a greater extent in the former, present-day diets go below normal requirements for vitamin A values, even though the money outlay for such a diet is relatively high. And it is to be presumed that the negro of the Southern cities has made a choice of better value and of probably relatively less expense in his selection of sweet potatoes and other cheaper, but more abundant carotene-containing plant products. Where the North Atlantic family buys only four pounds of sweet potatoes to 153 pounds of potatoes, the Southern negro buys in the ratio of 42 to 49: and his consumption of leafy green and yellow vegetables is to that of the white adult of the North Atlantic as 90 is to 75.

With vitamin A and other recognized deficiencies of the diets of the North Atlantic area in mind, we began last year to make a nutrition survey of a series of pregnant women in Philadelphia. There was no selection of the patients, who were attending prenatal clinics at the Presbyterian Hospital and at the Jewish Hospital. Women in all stages of pregnancy and degree of parity, at no particular season of the year were included. A nutritionist interviewed the women personally, instructing them how to record properly their food intake over a period of seven days. When the food records* were returned, all items were

FREQUENCY DISTRIBUTION OF VITAMIN A CONTENT
OF DIETARIES OF 123 PREGNANT WOMEN

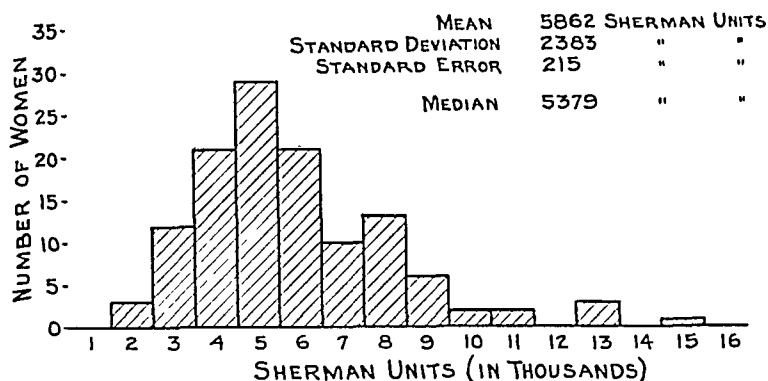


Fig. 3.—Frequency distribution of vitamin A content of dietaries of 123 pregnant women.

scrutinized and checked by the nutritionist during a second personal interview. Although some food records had to be discarded because they were incomplete or inaccurate, we feel that, obtained in the manner described, they furnish a reasonably good picture of the usual diet of these pregnant women.

The food records were then analyzed for their vitamin A values in Sherman units, as set forth in *Food Values of Portions Commonly Served*, First Edition, 1937, prepared by Bowes and Church.¹⁸ All the analyses in this report were computed in Sherman units, because data for average vitamin A values in the international units were not sufficiently complete or definite for our purposes. No conversion into international units was attempted because, as Munsell states, "... the derivation of a conversion factor is not a valid procedure. Any implied relationship must be considered as merely indicative."

The vitamin A intake in Sherman units is graphically shown in Fig. 3.

Inasmuch as the food records were computed in Sherman units, there was a need for vitamin requirements in pregnancy also expressed in Sherman units. The most complete ones found were those announced

*The forms used for the food analyses were patterned after those designed for teaching purposes at the Dental School of the University of Pennsylvania.

by the Philadelphia Child Health Society in October, 1938. They include the following standards:

Vitamin A	6,000-10,000	Sherman units
Vitamin B	900- 1,200	Sherman units
Vitamin C	100- 200	Sherman units
Vitamin G	600- 800	Sherman-Bourquin units
Vitamin D	800	International units

An analysis shows that 62 per cent of the vitamin A values of the food records studied were below the requirements for pregnancy as stated above.

The next step was to measure dark adaptation timing by means of an adaptometer and the test was performed as follows:

The patient was placed in a dark room and exposed for a measured time (three minutes) to a strong bleaching light of controlled intensity. During the exposure period, it was necessary to observe the patient's eyes to see that they were kept open. After the exposure light was extinguished, the patient touched a small knob on the instrument casing and fixed in darkness at that point. This is called tactile sense fixation. The fixation point was so located that the image of the test light fell upon a predominantly rod retinal area (about 20 degrees off the fovea).

Readings for the regeneration of the visual purple were made at given time intervals by increasing the intensity of the test light until it became just barely visible. The patient had not only to report when she saw the test light, but also the direction of its oblong form. This direction could be adjusted by the operator, and thus the veracity of the patient's report was checked.

The earliest manifestation of avitaminosis A is night blindness. It is now known that the ability to see in dim illumination is due to the visual purple, which is regenerated normally only when an adequate supply of vitamin A or its precursor is present. The physiology and pathology of avitaminosis A and dark adaptation have been discussed by Hecht¹⁹ and the diagnosis of latent avitaminosis A with the photometer has been described recently by Feldman.²⁰ A full discussion will be found in their contributions.

Ricketts²¹ tested 40 pregnant women with the Jean's biophotometer and found 16 classified as good, 17 fair, 3 poor, and 4 very poor. There was an opportunity to check 19 cases after administration of carotene in oil with obvious improvement. Two of his cases presented vitamin A deficiencies so severe they simulated toxemias of pregnancy. Both responded to vitamin A therapy.

Edmund and Clemmesen,³ in a study of 50 women with complicated pregnancies admitted to a municipal hospital in Copenhagen, found that about half of them presented "dysadaptation." This term they apply to pathologic or abnormally high light threshold reading. Their cases presented largely hyperemesis and pyelitis as indications for hospitalization.

We made readings in 123 pregnant women, and checked them, and an ophthalmoscopic examination was made to disclose any pathologic lesion of the eye. We have considered five minutes or less as normal readings.

The dark adaptation time in the group ranged from two to eleven minutes. The results are expressed graphically in Fig. 4. The analysis shows that 37.5 per cent of these women had an adaptation time delayed beyond the normal of five minutes.

As a result of finding deficient vitamin A values in such a high percentage of the women by both dietary analyses and dark adaptation time, an attempt was made to correlate the findings in the deficient cases (Fig. 5). In the group under study, no definite tendency is dis-

FREQUENCY DISTRIBUTION OF DARK ADAPTATION TIME OF 123 PREGNANT WOMEN

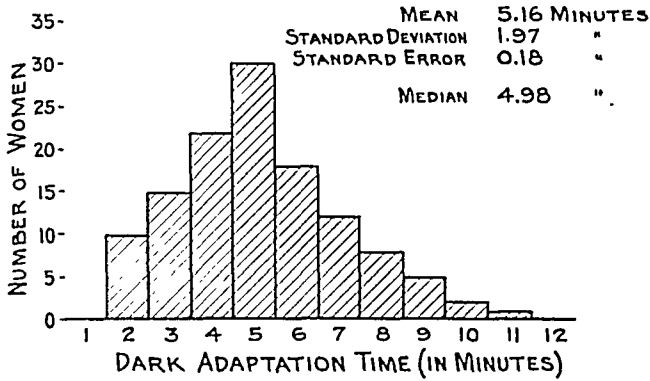


Fig. 4.—Frequency distribution of dark adaptation time of 123 pregnant women.

DARK ADAPTATION TIME AND VITAMIN A CONTENT OF DIETARY OF 123 PREGNANT WOMEN (EACH DOT REPRESENTS AN INDIVIDUAL)

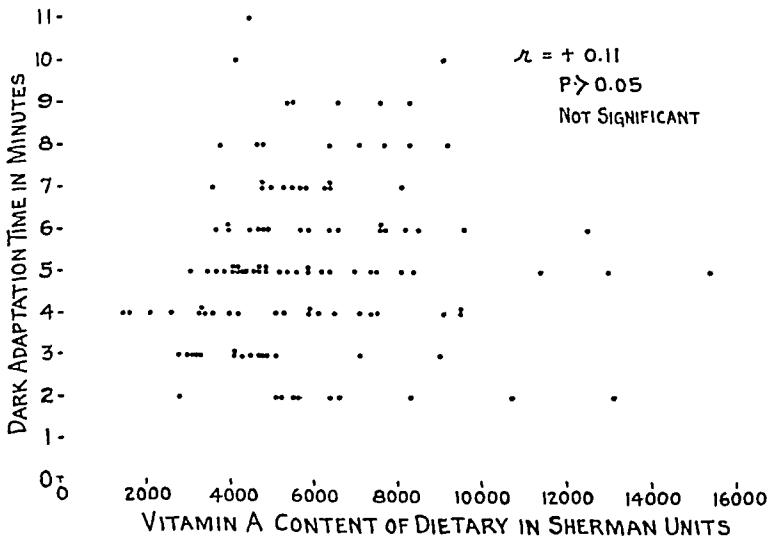


Fig. 5.—Scatter diagram showing correlation between dark adaptation time and vitamin A content of dietary of 123 pregnant women. (Each dot represents an individual.)

cernible for a higher vitamin A content of the dietary to be associated with a shorter dark adaptation time. In fact there is a slight positive correlation ($r = +0.11$) in the opposite direction, a higher vitamin A

content of the dietary tending to be associated with long dark adaptation times. However, the correlation coefficient is not statistically significant.

This type of correlation may be due to several factors. The vitamin A value of the diet may express a large proportion of carotene which may not be transformed. Other faults or variations in the physiology, of which we were ignorant, might have been present, and the human element in some instances, may have contributed to an unreliable record.

Thomson, Griffith, and others²² state the problem succinctly when they say, "The estimation of the amount of vitamin A or its precursors in food-stuffs has not yet reached a high degree of precision; published results for any one foodstuff show a wide range of variation, and it is not possible to be certain that published results are valid for the particular foods in any one diet. In experimental studies in which large doses of concentrates are given, this is not of importance, but it is of importance when attempts are made to correlate the vitamin A or carotene content of natural foodstuffs with dark adaptation."

Since sufficient amount of fat in the diet is considered essential for the proper transference and utilization of vitamin A, we have checked the fat content of the diet against the dark adaptation time in the series. The dietary fat value requirement was 91 Gm., as it was the average value. A fat value of such requirements, or above, and a normal, or shorter, dark adaptation time were present together in 40 per cent. A deficient dietary fat value and a delayed adaptation time were present together in 10 per cent. A deficient fat value and a normal, or more rapid, time were present in 23 per cent, and the remaining group with normal fat value and delayed time present, comprised 27 per cent. Here again the relationship is not sufficiently positive to be significant.

We have endeavored to determine the effect of supplemental administration of vitamin A upon the dark adaptation time. Oleum percomorphum,* was given to a group of women who had a dark adaptation time delayed beyond the generally accepted normal of five minutes. Twenty-eight women co-operated to an extent sufficient that the results may be reported.

The vitamin A was taken in a dose of 20,820 international units per day for seven days preceding the appointment for the second reading. At this time 21 showed reductions in the dark adaptation time ranging from one to six minutes. Of the remaining 7 women, 3 showed no reduction; and in the other 4 an increase of one minute was noted in 3, and an increase of three minutes in one. A third estimation was made seven to fourteen days after the second in these seven women and an improvement not noted at the second test was present in four. The assumption is that in these cases either the absorption or utilization was slower than usual due to some unknown delay in the mechanism concerned.

Of the 10 women in the seven-minute group, 9 showed reductions and one an increase. The findings in the group showing seven-minute readings have been expressed graphically in Fig. 6.

We regret that lack of time did not permit a control series without administration of vitamin A, and the same factor prevented a study of

*Furnished through the courtesy of Dr. Warren M. Cox, Jr., and the Mead Johnson Company.

the effect of the administration on a group of women whose adaptation time was better than normal.

That vitamin A may build up resistance to infection is an allowable claim. In this respect we have noted the febrile morbidities of the puerperium in 108 delivered women of the series with the vitamin A value of the diet.

There were 13 cases in which the temperature reached 100.4° F. (38° C.), twice in any two of the first ten days post partum. Eight of these had mild pelvic infections, five following forceps, premature delivery, toxemia, and packing for post-partum hemorrhage, and three following normal spontaneous delivery. In 7 cases the vitamin A value of the diet was low, in one it was above normal. In 3 cases of pyelitis the vitamin A value was low in only one. It was low in a case of mastitis, and in one anesthetic pulmonary complication after a cesarean section. However, many women with lower values did not develop any febrile morbidity.

There were two premature deliveries, one unexplained stillbirth, and one monster. In these four instances the vitamin A value was much below normal. The diets in this group were regarded as altogether markedly inadequate.

RESULTS OF 20,820 I.U. VITAMIN A DAILY FOR 7 DAYS ON ADAPTATION TIME OF 10 WOMEN. (INITIAL READING, 7 MINUTES)

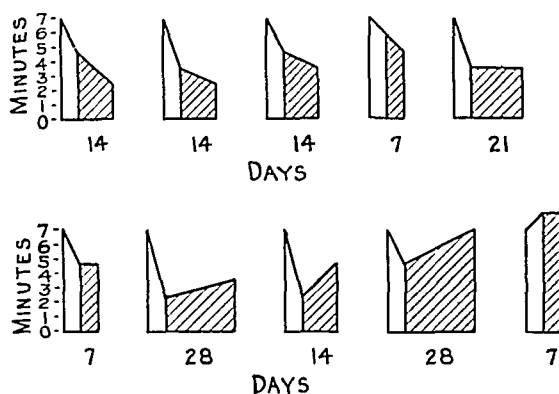


Fig. 6.—Results of administration of over 20,000 international units vitamin A daily for seven days on adaptation time of 10 women. (Initial reading, seven minutes.)

The relation of the weight of the baby to the vitamin A value of the diet permits no definite conclusions, as the series is relatively small.

In the 15 mothers of babies which weighed eight pounds or above at birth, 10 had values above 6,000 Sherman units and 15 below this figure. Of the 6 mothers whose babies weighed less than 6 pounds, only one had a dietary vitamin A value above 6,000 units.

Of the 104 babies, excluding a monster, a stillborn, and two prematures which died, 32 were on formula feeding when they were discharged from the hospital. Of the 32 mothers so represented the dietary vitamin A values were evenly divided above and below the requirement level of 6,000 Sherman units.

SUMMARY

In an analysis of the diets of 123 pregnant women, 62 per cent showed vitamin A below the requirement for pregnancy stated as 6,000-10,000 Sherman units.

The same women, together with 11 others for whom we had no food records, were tested for their dark adaptation time. Thirty-seven and one-half per cent gave readings delayed beyond the accepted normal of five minutes.

The correlation coefficient between the two types of analysis was not statistically significant.

A similar insignificant relationship was seen between fat intake and dark adaptation time.

The administration of vitamin A in concentrated form in 28 cases was followed by an improvement in the dark adaptation time in 75 per cent of the cases.

Ten of 13 delivered patients, with febrile morbidity in the puerperium, showed subnormal vitamin A intake. Many other women, however, with intakes below the requirement did not show febrile morbidity.

The series is considered too small to draw conclusions with reference to the birth weight of the baby and the mother's vitamin A consumption; nor was there any significant relationship between efficient lactation and vitamin A intake.

CONCLUSION

It appears from the above summary that while there is a marked deficiency of vitamin A content in the diet (62 per cent of 123 pregnant women), and a considerable deficiency in dark adaptation time (37.5 per cent), yet there is no close relationship between dark adaptation, the process of regaining clear vision in darkness, and the intake of vitamin A in the diet; nor between vitamin A intake and certain obstetric factors in a short series of cases.

We are grateful to Mrs. Anna DePlanter Bowes, Miss Elizabeth Pitney, and Dr. Olive Hoffman, for their valued technical assistance, and to the social service and dietary staffs of the two hospitals where the study was conducted, for their cooperation.

REFERENCES

- (1) *Munsell, H. E.*: Vitamin A—Methods of Assay and Sources in Food, The Vitamins, Chicago, 1939, Am. Med. Assn.
- (2) *Guilbert, H. R., and Hart, G. H.*: J. Nutrition 10: 409, 1935.
- (3) *Edmund, C., and Clemmesen, S. V.*: On Deficiency of A Vitamin and Visual Dysadaptation, London, 1936, Oxford University Press.
- (4) *Booher, L. E., Collison, E. C., and Hewston, E.*: Quoted by Stiebeling and Phipard.
- (5) *Stiebeling, H. K., and Phipard, E. F.*: Diets of Families of Employed Wage Earners and Clerical Workers in Cities. U. S. Dept. Agriculture, Circular No. 507. Washington, 1939, Govt. Printing Office.
- (6) *Gaetgens, G.*: Arch. f. Gynäk. 164: 398, 1937.
- (7) *Aschoff*: Verhandl. d. deutsch. Path. Gesellsch. 27: 145, 1934.
- (8) *Ellison, J. B., and Moore, T.*: Biochem. J. 31: 165, 1937.
- (9) *Dann, W. J.*: Biochem. J. 28: 2141, 1934.
- (10) *Sure, B.*: J. Agric. Research 37: 87, 1928.
- (11) *Mason, K. E.*: Anat. Rec. 58: Supp. No. 4, 80, 1934.
- (12) *Hart, G. H., Mead, S. W., and Guilbert, H. R.*: Proc. Soc. Exper. Biol. & Med. 30: 1230, 1933.
- (13) Human Requirements for Vitamins, Am. Public Health Assn. Yearbook 35: 69, 1934.
- (14) *Bussan, A.*: Rev. franç. de pédiat. 10: 413, 1934.
- (15) *Moore, T.*: Biochem. J. 31: 155, 1937.
- (16) Report on Physiological Bases of Nutrition: League of Nations Health Comm. Tech. Commission, London, 1935.
- (17) *Ross, R. A., Perlzweig, W. A., Taylor, H. M., McBryde, A., Yates, A., and Kondritzer, A. A.*: AM. J. OBST. & GYN. 35: 626, 1938.
- (18) *Bowes, A. DeP., and Church, C. F.*: Food Values of Portions Commonly Served, Philadelphia Child Health Society, Philadelphia, 1937.
- (19) *Hecht, S.*: Dark Adaptation and the Diagnosis of Avitaminosis A. Nutrition: The Newer Diagnostic Methods. New York, 1939, Milbank Memorial Fund.
- (20) *Feldman, J.*: The Use of the Photometer in Detecting Latent Avitaminosis A. Nutrition: The Newer Diagnostic Methods. New York, 1939, Milbank Memorial Fund.
- (21) *Ricketts, W. A.*: AM. J. OBST. & GYN. 38: 484, 1939.
- (22) *Thomson, A. M., Griffith, H. D., Mutch, J. R., Lubbock, D. M., Owen, E. C., and Legaras, G.*: Brit. J. Ophth. 23: 697, 1939.

VITAMIN A IN PREGNANCY

I. AVERAGE CAPACITY ACCORDING TO THE FELDMAN ADAPTOMETER

JOHN C. HIRST, A.B., M.D., F.A.C.S., AND ROBERT E. SHOEMAKER, B.S.,
M.D., PHILADELPHIA, PA.

THE identity, chemistry, physiology, and pathology of vitamin A have been well studied and numerous reports are found in the literature, but only in recent years (1934) have blood assay and photometric methods of determining vitamin A capacity been generally available. Since that time, the vitamin A levels of numerous groups of patients have been studied, although mostly under variable methods and conditions, not including pregnancy.

It has been our purpose in this study to attempt to establish via photometric tests the average vitamin A capacity through pregnancy, and the frequency, degree and significance of deviations from this "normal."

PRINCIPLES

The fat soluble vitamin A is a derivative of the carotinoid group of pigments from plants from which the animal body is able to metabolize vitamin A. This vitamin is stored in the body principally in the liver, so that abnormalities of digestion, anemia,¹ and liver disease² may interfere with absorption and storage of the vitamin. Thus actual vitamin A deficiency may arise in association with vomiting, chronic diarrhea, biliary duct obstruction, pancreatic dysfunction, celiac disease, etc.

The process of achieving more or less vision in the dark, called "dark adaptation," is dependent upon supply or level of vitamin A, and it is established that one of the earliest functional changes due to vitamin A deficiency is decreased ability for dark adaptation resulting in night blindness,³ commonly experienced as unusual difficulty in locating seats in motion picture theaters, and in dangerous temporary loss of vision while driving an auto against another's headlights.

Persons showing latent or actual night blindness are also apparently predisposed to urinary infection and calculus,¹ respiratory infection, certain skin affections⁴ and possibly to puerperal infection.⁵

Light enters the eye and falls upon the retina where it is absorbed by the photosensitive visual purple of the rods which are concerned with vision under dim illumination. The visual purple photosensitive pigment is a protein combination with vitamin A, and with absorption of light is broken down, initiating the nerve impulse of sight in darkness. However, normally, this visual purple is rapidly resynthesized from reserve of vitamin A, the rapidity being dependent upon the amount of vitamin A available. Ample vitamin A therefore means rapid dark adaptation as well as good night vision, but deficiency of vitamin A results in delayed adaptation or night blindness.

If the visual purple is bleached or decomposed by a definite and constant quality and intensity of light for a standard period of time in a dark room, then the rapidity of the eyes to recover ability to see a definite intensity of dim light becomes a measure of the person's dark adaptation, and consequently his vitamin A level of the body, the recovery period being designated as the dark adaptation time. Various apparatuses have been devised to establish adaptation time, including the questionable biophotometer,⁶ which has proved variable by reason possibly of insufficient light to completely bleach the visual purple; rheostat light control which

changes color of the light (as well as intensity); difficulty in observing patient; and interference of macular vision.

METHOD

The patient is placed in a totally darkened room and the eyes exposed to the adaptometer's bright standard intensity of light for exactly three minutes. This light is then turned off, and in its place a constant dim linear light of definite intensity appears 20 degrees off the macula where the rods predominate. A stop watch is started and the patient told to tell the examiner as soon as the dim linear light becomes visible, the time interval being recorded. As a check upon the patient, the angle of the dim light is changed from horizontal to vertical or vice versa and the patient asked to indicate in which direction it is pointing. This prevents false readings in that it proves to the examiner that the patient has actually seen the light. The adaptation time is then read in minutes and seconds.

With this instrument it has been determined that a light threshold adaptation time of five minutes or over is pathologic and indicative of vitamin A deficiency, whereas an adaptation time below five minutes is evidence of normal vitamin A level. We have found the Feldman adaptometer particularly satisfactory for prenatal observation because of the ease of operation, comparative rapidity of the test, and fairly uniform results according to frequently repeated tests on our normal pregnancies.

MATERIAL

The Preston Retreat is an endowed institution for the confinement of "indigent married women of good character" who are residents of Philadelphia and Delaware Counties. Capacity is limited, and because there are always more applicants than can be accepted, a certain degree of selection is possible. There are no colored patients and the majority are of so-called American stock, factors which result in a rather high type of clinic patient. This we feel is important, representing the largest proportion of women in the country, namely, the lower middle class.

Medically, the patients are carefully and adequately followed throughout their pregnancy and confinement, and social service cooperation is exceptionally good, including home visits to every patient.

This study was begun in March, 1939, upon a group of 200 uncomplicated patients, one-third nulliparas and two-thirds multiparas, all of whom have been delivered. Adaptation times were taken by the same technician between 9:30 and 11:30 A.M., daily, at various intervals throughout pregnancy and upon many at the six weeks' post-partum visit, and some much later. All patients who showed an abnormal adaptation time, i.e., five minutes or over, were examined by an ophthalmologist to determine whether the high reading might be due to ocular pathology. It may be stated here that none was found.

RESULTS

Fig. 1 shows the average prenatal and postnatal adaptation times of 200 registered clinic patients as derived from 880 tests. The highest and lowest readings were, respectively, 480 and 15 seconds, but the greatest divergence in any one case was 345 seconds (from 6 minutes—45 seconds to 1 minute). There were only 18 (9 per cent) readings of five minutes or over and 4 (2 per cent) of these were accounted for by women with high primary single, presumably false, estimates, probably due to the subjective nature of the procedure since subsequent tests were all low. On the other hand, 3 patients (1½ per cent) gave original low readings followed by increases approaching or over five minutes on only one occasion, possibly indicating a pregnancy trend toward avitaminosis A, but more likely subjective temporary fatigue or emotion. The general downward or improvement trend may be attributed to improved prenatal condition, or less likely to the influence of the summer season during which the latter half of the tests were performed.

Fig. 2 shows the distribution of reading by weeks, not including 14 observations as late as eight to thirty-eight weeks post partum. The open circles repre-

sent adaptation times of the first 100 cases, and the solid circles indicate readings from the second 100 patients, showing a tendency to lower results, i.e., higher vitamin A as pregnancy advances.

Forty-four per cent of the "normal" patients gave repeated adaptation times not varying more than sixty seconds, excepting the first reading, among which 4 per cent were almost constant. The remaining 56 per cent varied more than sixty seconds, but not nearly to the degree of the pathologic and borderline groups described later.

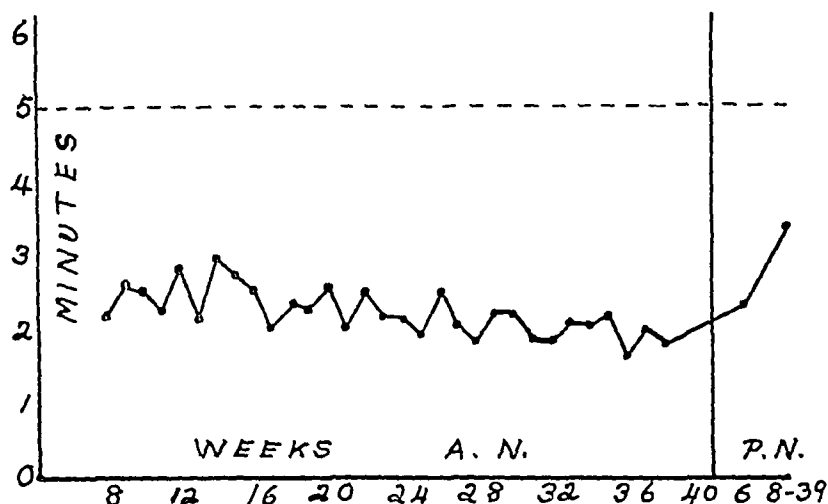


Fig. 1.—Mean dark adaptation of 200 average pregnancies, showing increasing vitamin A capacity.

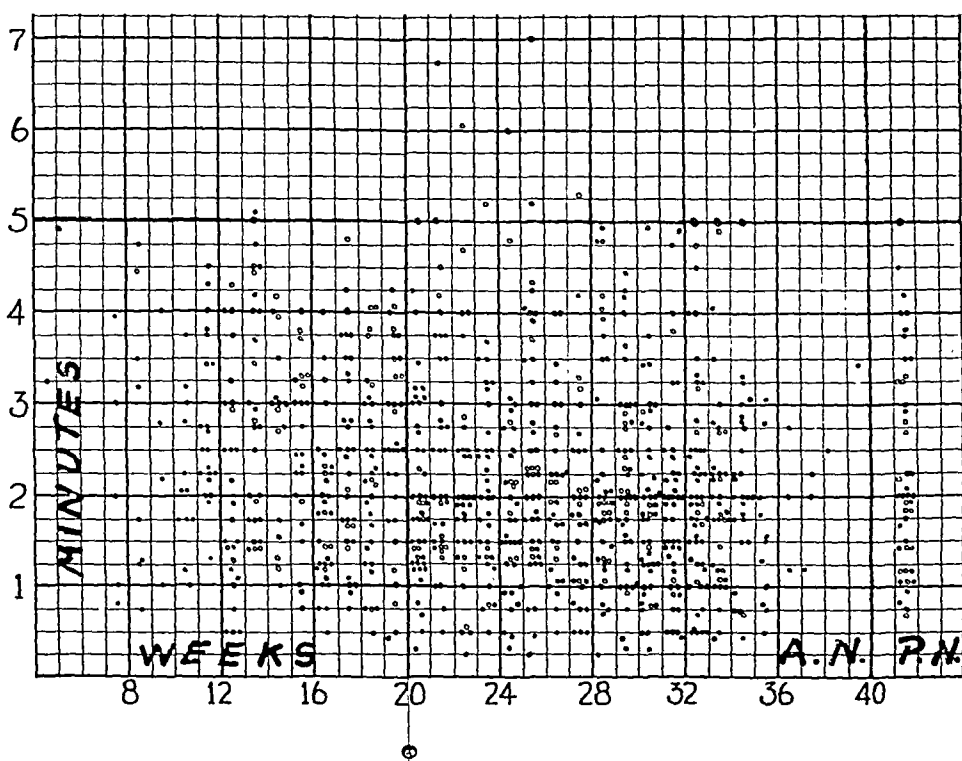


Fig. 2.—Distribution by gestational weeks of 880 adaptometer readings.

Fig. 3 includes the entire curves of 6 cases (3 per cent) considered pathologic, based on 2 or more readings of five minutes or over, apparently not entirely due to pregnancy, and none of serious degree or constantly above the abnormal limit.

Fig. 4 shows 8 cases (4 per cent) of temporary borderline abnormal type, each characterized as those of the preceding group by rather wide excursions, difficult to explain.

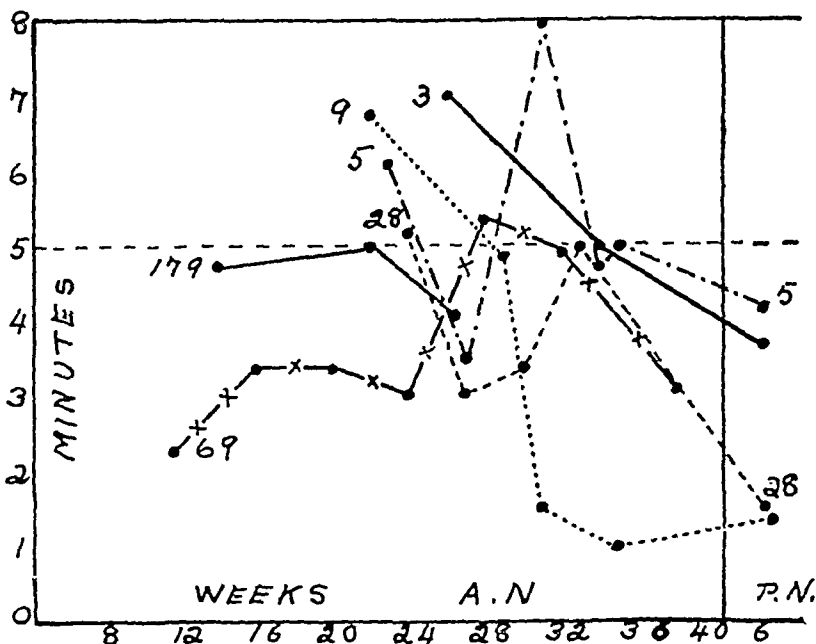


Fig. 3.—Curves of 6 (3 per cent) pregnancies with delayed adaptation times of five minutes or over, 2 or more times.

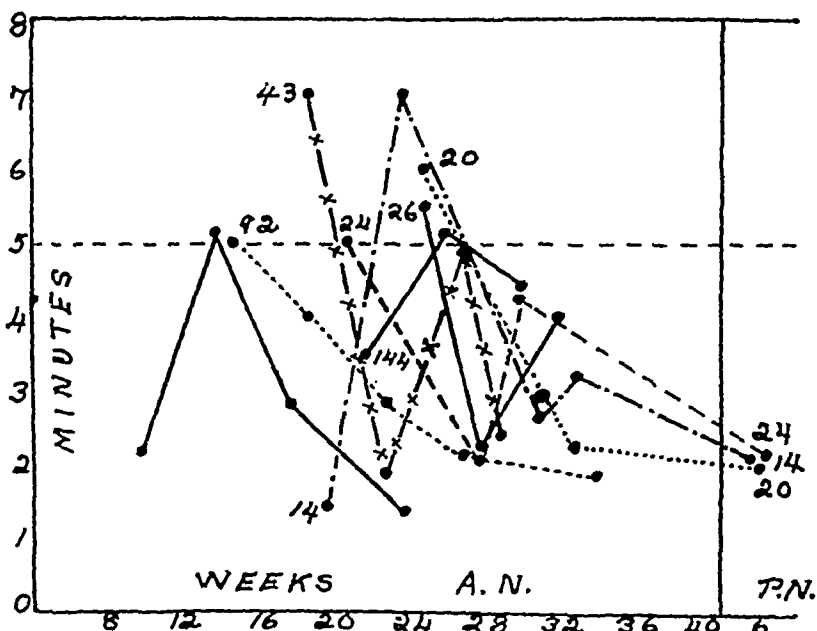


Fig. 4.—Curves of 8 (4 per cent) "borderline" pregnancies with at least one delayed adaptation time about five minutes, excluding 4 cases of single primary high (false) readings.

In our series, there was no apparent relation between vitamin A deficiency and complications of pregnancy, labor and the puerperium, particularly with regard to respiratory, urinary, and puerperal infection.

It is clear that single test estimations of vitamin A level in patients are acceptable only if pathologic adaptation times are rechecked and verified several times within a short period. This should apply particularly where therapy is contemplated and again in any attempt to establish deficiency percentage by running single tests on large numbers of patients. It may also be added that for obvious reasons, the intelligence of the patient is a big factor, tending in single tests to produce a high amount of apparent but unreal vitamin A pathology.

SUMMARY AND CONCLUSIONS

1. Two hundred registered pregnant women in the clinic under good prenatal control were repeatedly tested for vitamin A capacity by the Feldman adaptometer.

2. Nine per cent showed at least one reading above five minutes, but only 3 per cent showed repeated abnormal readings and were judged deficient in vitamin A, and 4 per cent were "borderline."

3. Vitamin A deficiencies occurring in average pregnancy tend to be mild, and not entirely related to pregnancy.

4. There is a general tendency to improvement in normal vitamin A status during pregnancy, as well as less frequent deficiency, due either to the summer season, or most likely to good prenatal care.

5. There were no significant medical and/or obstetric complications among the small number of deficient women.

6. Many more pregnancies must be studied before absolute reliance may be placed upon a subjective test for vitamin A.

In our series we made use of the adaptometer designed by J. B. Feldman, M.D., and provided by Wm. J. Ezickson, M.D., to whom the authors are also indebted for criticism and advice.

REFERENCES

- (1) *Ezickson, W. J.*: Urol. & Cutan. Rev. 42: 820, 1938. (2) *Idem*: J. Lab. & Clin. Med. 24: 836, 1939. (3) *Feldman, J. B.*: Arch. Ophth. 22: 595, 1939. (4) *Frazier, C. N., and Hu, C.*: Arch. Dermat. & Syph. 33: 825, 1936. (5) *Torrance, Calvin C.*: AM. J. OBST. & GYNEC. 27: 868, 1934. (6) *Steininger, G., Roberts, L. J., and Brenner, S.*: J. A. M. A. 113: 27, 1939. (7) *Feldman, J. B.*: Arch. Ophth. 18: 821, 1937.

500 NORTH TWENTIETH STREET

Pagniez, Ph.: The Treatment of Pruritus Vulvae by the Local Injection of Histamine, Presse méd. 47: 1359, 1939.

The writer reviews Lavandhomme's experience with the use of local injection of histamine for pruritus vulvae. In 5 of 6 cases persisting from several months to several years, the injection of histamine produced rapid and apparently lasting relief to the patient. Lavandhomme uses 1 c.c. ampoules, containing 0.005 Gm. of histamine bichlorhydrate. At the first visit he makes 20 intradermal injections in the labia majora. During the following visits, the site of the injections is progressively extended toward the labia minora and the vaginal mucosa. He observed in 2 cases the disappearance of early atrophic or kraurotic vulvar lesions.

The author feels that this mode of treatment may well be tried in the more rebellious cases of pruritus vulvae.

CLAIR E. FOLSOME.

PREGNANCY PYELONEPHRITIS IN RELATION TO RENAL DAMAGE AND HYPERTENSION*

A CLINICAL STUDY OF 45 CASES OF PYELONEPHRITIS MORE THAN FIVE TO TEN YEARS AFTER THE INFECTION

E. GRANVILLE CRABTREE, M.D., AND DUNCAN E. REID, M.D.,
BOSTON, MASS.

(From the Urological and Toxemia Services of the Boston Lying-in Hospital)

THAT a causal relation should be recognized between pyelonephritis and renal insufficiency and hypertension is indicated by recent publications. This interrelation is further confirmed by autopsy findings, which show either healed or still active pyelonephritic lesions in a high percentage of hypertension cases. This belated recognition of what seems to be a fact is explainable chiefly on the ground of chronicity of pyelonephritic lesions, their tendency to persist or to recur, and their progressive nature, which makes an estimate of the degree of damage of the kidney by the initial injury more obvious long after injury than at the time it occurs. The picture has been further confused and recognition of injury to the renal cortex missed, particularly by urologists, because attention has been concentrated on, and a causal significance assigned to, the more obvious and easily demonstrable injuries and defects of the conduction channels of the kidney, the pelves, and ureters. Until more recent years, there has been no provision for continuity of observation of a case by the same physicians over the long course which we now recognize that pyelonephritis runs.

Both in pregnancy infections of the urinary tract and in those in the puerperium there is little evidence, in most cases, of renal insufficiency, and where such insufficiency has been demonstrated, there is prompt return of the kidneys to apparent normal function in pregnant women. These apparent facts tended to strengthen the point of view that pyelonephritis is a transitory affection. Obstetric and urologic practice have been dominated by this point of view to such an extent that preservation of the fetus, even in severe cases of pyelonephritis of pregnancy, has been made paramount unless immediate danger of disastrous results to the mother was indicated. The newer concept of the severity of remote effects of pregnancy pyelonephritis now threatens a reversal of policy. Some writers are prepared to advocate interruption of pregnancy on evidence which obstetricians consider inadequate (Peters¹). The strongest evidence so far

*A portion of the funds for this research was provided through a gift made by Mrs. Harriet Morse Sturgis. Grateful acknowledgment of this contribution is here recorded.

A second portion of the necessary funds was supplied through the kind offices of Dr. H. M. Teel from the funds of the Department of Child Hygiene of the Harvard School of Public Health.

produced for making a practice of routine interruption of pregnancy for pyelonephritis is from medical data obtained from the study of terminal hypertension cases and autopsy material.

This policy, if adopted now, would be unsupported by evidence of the state of health of these women with pregnancy pyelonephritis over long intervals admittedly existing between the initial injury and the terminal medical surveys and autopsy examinations. Does pyelonephritis shorten the lives of such women or merely modify the data on the death certificate? Do they evidence ill health throughout their lives, after pregnancy infections, or are their kidneys adequate for normal living in spite of injury until terminal changes, possibly due in part to other factors, end in the development of renal insufficiency or rise in blood pressure which quickly closes the story somewhere near the average age for death for women? In what percentage of women who have had pyelonephritis in pregnancy, and in what types of the disease, does complete recovery from the injury occur? In what percentage of the cases has there been set in motion, as a result of infection, those vicious factors which accomplish their destruction in the course of a few years? Until some of these questions have been answered through clinical study of apparently healthy women who have had the disease, a radical policy of interruption of pregnancy for pyelonephritis is no more logical than a policy which preserves the pregnancy at any cost to the mother short of death.

Hage² furnishes striking data on pyelonephritis and contracted kidney in autopsy material. In 9,888 routine autopsies performed between 1931 and 1937, 598 patients showed pyelonephritis. Sixty-nine patients showed contracted kidneys. Pyelonephritis was about equally distributed among women and men. Contracted kidney was found more often among women than men. The commonest causal factor in men seemed to be prostatism, and pyelonephritis was found more often in later life. In women, he considered that pregnancy accounted for the occurrence of the condition in a large number of cases. There was evidence that prostatism in men and pregnancy in women were responsible for a high percentage of the pyelonephritis which he found at autopsy, and these two conditions seemed to be the main diseases through which numerical balance in frequency of occurrence of pyelonephritis between the sexes was maintained.

In view of the general considerations above, it has seemed advisable to investigate a group of apparently healthy women from our clinic, the nature of whose illness at the time of the initial pyelonephritis was known to us, since they were cared for in our hospital, to determine whether there was evidence of renal insufficiency and hypertension.

The material employed in this study consisted of 45 cases of pregnancy pyelonephritis, in which the pyelonephritis occurred from five to ten years before the investigation was undertaken. These cases represent the usual variation in incidence of the disease. Some were ante-partum cases, some were post-partum cases, and in others there were manifestations of the infection both in the ante-partum and the post-partum state. In some, there were no further pregnancies after the infected pregnancy. In others, there were from one to five subsequent pregnancies. In some of the subsequent preg-

nancies, there were manifestations of infection. In others, there were subsequent pregnancies without signs of infection.

The cases were divided into three groups, according to severity of the pyelonephritis symptoms demonstrated. Group I consisted of 14 cases in which there were pyuria, bacteriuria, and little or no febrile manifestations. If fever occurred, it was of but a few days' duration, after which the patient continued in apparent good health, but remained for the most part infected throughout the remainder of the pregnancy. Group II consisted of those cases in which there was some febrile reaction and more severe symptomatology, but the patients all were tractable to treatment and finished the pregnancy in good general condition. There were 12 cases in this group. Group III consisted of 19 cases. These were all severe febrile reactions to the infection and most of them required cystoscopic treatment and even induced labor before the subsidence of the acute symptoms was obtained. Unilateral infections were present in all the groups. One case was included in which a post-partum infection proved to be only cystitis, resulting from catheter management of bladder difficulties which followed delivery. In this case, it is of interest to note the normal response to all tests, in contrast to a tendency for some unilateral mild cases to show evidence of subnormal response to some or all tests employed. There were no cases in which there was evidence from pyelographic study of the condition of the kidneys previous to the childbearing period. No cases were included in which it was probable that pre-existing renal pathology was present previous to pregnancy, as judged from the appearance of the pyelography at the time of this survey. Three cases were in the early months of a subsequent pregnancy when re-examined. In three cases, definite toxemic symptoms occurred in the course of the pregnancy, in addition to pyelonephritis. One of these cases was seen less than five years after infection, but was included because of a desire to contrast the present condition of the patient with the pyelonephritis group as a whole. The other two toxemic patients had already died.

Method of Study Employed

As far as it was possible to enlist the cooperation of the patient, all patients were tested by seven measures. These were: (1) Sufficient number of blood pressure readings to determine hypertension; (2) albumin determination on catheter urine; a wet sediment was also examined for pus, erythrocytes, and bacteria; (3) stained catheter urine sediment to determine bacterial content; (4) culture from catheter urine; (5) intravenous phenolsulfonephthalein excretion in four fifteen-minute periods for a total excretion period of one hour; (6) intravenous diodrast with special attention to the time at which the best plate appeared in the course of the pyelography; (7) nonprotein nitrogen (whole blood) determination. In three instances, cystoscopic study and separate determination of function of the kidneys was done. Sulfanilamide therapy was employed in an attempt to clear the infection, so that a redetermination of the renal adequacy might be made after the infection had been cleared. In one of these cases, a rise in nonprotein nitrogen accompanied the administration of sulfanilamide and caused discontinuance of the treatment before the infection had been cleared. Similar behavior was noted in another case of renal deficiency, not in this series, when sulfanilamide was administered.

GROUP I. FOURTEEN CASES STUDIED

Grouped according to time of infection in pregnancy:

Ante-partum infections	4
Post-partum infections	7
Ante-partum and post-partum infections	3
2 patients showed pre-eclamptic symptoms in addition to pyelonephritis.	

Grouped according to parity:

First pregnancy	5
Second pregnancy	2
Third pregnancy	1
Fourth pregnancy	2
Fifth pregnancy	2
Sixth pregnancy	1
Not recorded	1

Grouped according to side involved: 6 cases cystoscoped.

2 ante-partum unilateral; 1 right, 1 left sided.
2 post-partum bilateral
2 both ante-partum and post-partum bilateral (1 cystitis only)

Grouped according to subsequent pregnancies:

Sterilized for apparent renal deficiency soon after delivery	1
1 subsequent pregnancy (One had infection but mild symptoms)	2
2 subsequent pregnancies	3
3 subsequent pregnancies (without infection)	1
The remaining women had no subsequent pregnancies.	

Cystocele was present in 2 who were wearing pessaries. A third patient had been operated upon for cystocele. This percentage of cystocele is noteworthy, because for many years we have been checking residual urine to determine bladder condition, and it is rare that cystocele is noted near to delivery. The finding is in accord with the point of view expressed by gynecologists that cystocele develops late, although due to birth canal injury.

Blood Pressure Findings.—Only 3 patients, and these not the pre-eclamptics, had blood pressures above 150/90. One with a reading of 160/92 had had ante-partum infection with a single pregnancy, her fifth. She had a normal phthalein excretion, concentrated to 1.018, and there was no evidence of infection at time of the examination. She had had two pregnancies without recurrence of the infection. The original infection was bilateral. Later the patient was operated upon for renal calculus elsewhere, and finally had a thyroidectomy. A second patient had an infection with the fifth pregnancy, but the infection did not occur with subsequent pregnancies. The blood pressure was 190/130. There was a deficiency in the phthalein output. The urine was concentrated to 1.024. She was still infected, and there was unsatisfactory filling of the kidneys and ureters on intravenous pyelography, but no symptoms of any kind. The third patient was infected in her second pregnancy. She had had no subsequent pregnancies but was considered infected, with much pus and mixed infection. The urine was concentrated to 1.022. Later she was found (elsewhere) to have stones and hydronephrosis of the left kidney. The right kidney was uninfected at the time of study previous to lithotomy for the stone.

Concentration of Urine Test.—Three patients concentrated their urines to 1.025 or above. Eleven patients did not concentrate to 1.025.

Nonprotein Nitrogen.—In none of the cases was nitrogen retained. The highest figure obtained was 36 mg. per 100 c.c. of blood (whole blood method).

Intravenous Pyelography.—Eight patients had intravenous pyelography. In one, the cystitis case, the best plate was obtained at five minutes after injection of the

dye. In 6, the best plate was seen at fifteen minutes, and at thirty minutes in the other. A definite reluctance to fill on the side with the most severe infection was noted in all of these cases, if there was any difference at all between the kidneys.

Intravenous Phthalein Test.—In 8 of the 14 cases, there was evidence of delay in output of the dye, so that the first fifteen-minute output was below 25 per cent and was usually below that of the second, and sometimes of the third, interval of excretion. The excretion curve for the whole group is indicative of this relation (Fig. 1).

Albumin.—Albumin was not present in the catheterized urines of any of this group.

Wet Unstained Sediment Examination.—Only one of the 14 patients showed frank pus in the urine. Red blood cells were not noted. Five patients showed bacteria in sufficient numbers in the unstained smear to be considered to represent infection. Cocci are less readily recognized by this method than bacilli.

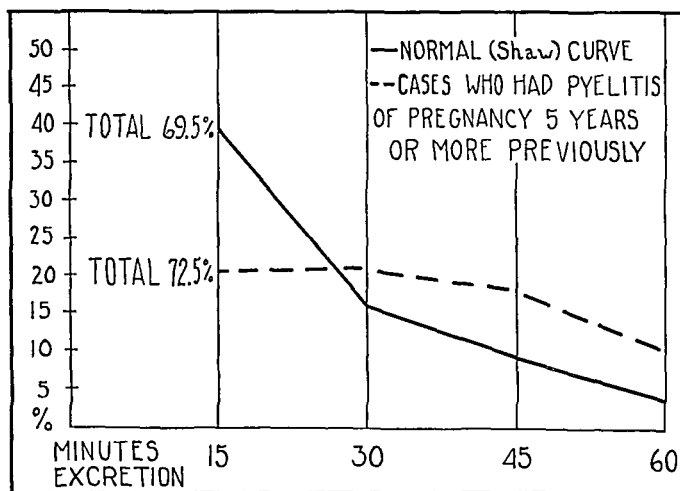


Fig. 1.—A composite chart of phenolsulfonephthalein excretions for the cases in this series. It is to be noted that the total secretion is not diminished for the group as a whole. There is, however, flattening of the curve by delay of the major portion of the output beyond the first fifteen minutes.

Stained Preparation From the Sediment and Culture.—Stained sediment and culture agreed in establishing the diagnosis in 5 patients as being infected and 2 as uninfected. Three cases yielded bacilli, culturing *B. coli*; 1 a mixed infection of *B. coli* and staphylococcus; and 1 staphylococcus only. Cultures showed 7 other cases to contain bacteria. In stained smears, rare bacteria were sometimes found. These cases showed the following findings:

<i>Micrococcus catarrhalis</i>	2
Rare colonies of <i>Streptococcus fecalis</i>	2
<i>Staphylococcus albus</i> and Döderlein's bacillus	1
Gram-positive and gram-negative unidentified bacilli	1

These six cases were considered as probable contaminations and not infections.

Gross evidence of abnormality, as shown by x-ray and intravenous pyelography.

Calculus	3
Pelves large and ureters tortuous	2
Either small renal shadows or caliceal evidence of contracted kidneys on one or both sides	4
Very poor filling of both pelves and ureters	2
Ureters filled so far down toward bladder as to suggest obstruction	2
Aberrant vessel small hydronephrosis	1

In recording these results of x-ray, the numerous lesions noted occurred in 4 of the 8 cases in which pyelography was done.

In 3 outpatient cases and one house case, the infection was cleared without difficulty by administration of sulfanilamide. One patient in this group, in whom a questionable diagnosis of pre-eclampsia, in addition to pyelonephritis, had been made during pregnancy, and who later had moderate renal deficiency to phthalein excretion, showed a rise of nonprotein nitrogen from 35 mg. per 100 c.c. of blood to 58 mg. on the third hospital day of administration of 40 gr. daily of sulfanilamide without concentration of urine. The nonprotein nitrogen began to decrease on discontinuing the drug and returned to normal within the next few days.

GROUP II. MODERATELY SEVERE INFECTIONS (12 CASES)

Grouped according to time of infection in pregnancy:	
Ante-partum infections	6
Ante-partum and post-partum infections	6
None were toxemic	
Grouped according to parity:	
First pregnancy	4
Second pregnancy	3
Third pregnancy	2
Fourth pregnancy	2
Eighth pregnancy	1
Ninth pregnancy	1
Tenth pregnancy	1
Eleventh pregnancy	1
Twelfth pregnancy	1
Grouped according to side involved:	
Bilateral	5
Unilateral	5
Not recorded	2
Grouped according to subsequent pregnancies:	
Without recurrent pyelonephritis	1
Died of cancer of lung soon after infected pregnancy.	
It was noted that the kidneys appeared to be normal.	1
Record of 5 infected pregnancies, subsequent pregnancy with pyelonephritis cared for elsewhere, 3 other pregnancies were unknown	1
3 subsequent pregnancies, 2 with elevated blood pressure	1
No further pregnancies	6

Blood Pressure Findings.—Four of the 12 patients had blood pressure readings above 150/90 at the time of examination. The first had a pressure of 150/100. She was primiparous at the time of pyelonephritis, with no subsequent pregnancies (1930), and showed delayed output of phthalein, concentrated to 1.022. There were albumin, pus, and a definite infection with *B. coli*. X-ray films made elsewhere reported her as showing chronic pyelonephritic changes. The second case, 160/100, showed normal phthalein excretion, concentrated to 1.027, was uninfected, was a bilateral pyelonephritis in 1931 in her third pregnancy. She had three subsequent pregnancies, one of which was reported from another hospital to have been accompanied by a rise in blood pressure. In the following pregnancy she also had high blood pressure. The third patient, 156/94, had normal phthalein output; concentrated to 1.026, was uninfected, and had a single infected pregnancy, with both sides involved, in 1930. There were no subsequent pregnancies. The fourth patient, 160/100, refused intravenous phthalein test; concentrated to 1.026, was infected in the fourth pregnancy, 1929, and had no subsequent pregnancies. She now has a stone.

Concentration Test.—Three of 8 patients tested did not concentrate to 1.025. All eight concentrated to 1.020.

Nonprotein Nitrogen Test.—Six patients tested. All were normal.

Albumin.—Albumin was present in but 1 patient of the 12. This patient is the first one in the preceding paragraph on blood pressure findings.

Wet Unstained Sediment Examination.—Two of 9 patients examined showed pus, and 1 other showed bacteria. No red cells were reported.

Stained Smear Preparations and Cultures.—Three of 9 patients showed bacteria and 6 were negative. Of the 3 with bacteria, 2 were bacilli and 1 coccus. Of the 10 patients in whom there were cultures, 2 showed *B. coli* and 1 *Staphylococcus aureus*. These were the same patients who were reported positive in stained smears. Seven were negative to culture. Of the 4 hypertension cases, 3 were uninfected. There were no doubtful infections or questions of contamination in these patients.

Intravenous Phenolsulfonephthalein Excretion.—Excretion of phenolsulfonephthalein was tested in 6 of the 12 patients. It was normal in 4 instances and abnormal in 2. The readings in the first of the patients considered abnormal were 10 per cent, 15 per cent, 35 per cent, and 10 per cent for a total of 70 per cent in one hour after intravenous injection of the dye. In the other patient, the excretion was 20 per cent, 30 per cent, 25 per cent, and 10 per cent for a total of 83 per cent. These patients show delay and not a deficiency of excretory ability.

Intravenous pyelography was done in but 5 cases. In 2, the pyelography was done elsewhere and was reported negative. In the 3 patients in whom we did pyelography, there were stone and kink in one, stone in another, and in the third patient there was poor filling of the kidney which had been the site of a unilateral infection.

GROUP III. SEVERE INFECTIONS, 19 CASES

Grouped according to time of infection in pregnancy:

Ante-partum infections	9
Post-partum infections	2
Ante-partum and post-partum infections	7
Not stated	1

Grouped according to parity:

First pregnancy	11
Second pregnancy	1
Third pregnancy	3
Fifth pregnancy	1
Ninth pregnancy	1
Twelfth pregnancy	1
Unknown	1

Grouped according to initial lesion (cystoscopically controlled):

Bilateral lesions	8
Unilateral lesions	7

There was stone also in 1 of the patients at the time of initial examination, congenital absence of 1 kidney in another, and in 1 unilateral case infection was confined to the left side.

Grouped according to subsequent pregnancies:

1 normal pregnancy	9
Now pregnant (one at 3 and other at 4 months, without trouble)	2
2 pregnancies (one abortion from pyelonephritis, the other uninfected)	1

Three of these patients had pregnancy toxemia in addition. One patient with toxemia and bilateral pyelonephritis, both ante partum and post partum in the first pregnancy, 1930, died of hypertension, "chronic nephritis" and renal failure in 1936. A second patient had ante-partum pyelonephritis and toxemia in the first pregnancy, 1931, had a second pregnancy which was said to be free of complications, and died of acute cardiac failure. She collapsed and died suddenly at a relief station in 1937. The third patient, who has not rightly been included in this group, since but three years have elapsed since her infection, was included that we

might have the data on a case similar to the two who died, but at a time antedating death. She was primiparous, with bilateral infection, in 1936. There have been no subsequent pregnancies. Blood pressure, 165/106. Phthalein output 10 per cent, 13 per cent, 9 per cent, and 7 per cent for a total of 39 per cent in one hour after intravenous injection of dye. Nonprotein nitrogen was 40 mg. per 100 c.c. of blood, by whole blood method; concentrated her urine to 1.016. She is still infected with hemolytic *Staphylococcus aureus* and showed three-plus albumin and hyaline casts. There was no retention of the intravenous media in the kidneys sufficient to cast a shadow at all, with only a trace of dye appearing at thirty minutes, but insufficient to outline any part of the kidney pelvis accurately. This patient was studied intensively at the Beth Israel Hospital.

The findings were as follows: She was 28 years old; hypertension and swelling of the legs were apparent three months following delivery. On rest in bed, the blood pressure readings ranged near normal; the highest reading was 135/70. The edema and discoloration of the legs persisted even though she remained in bed.

Laboratory Data.—During the hospital stay, on catheter specimens, patient showed very slight trace to trace of albumin with 3 to 5 white blood count and a rare red blood count. Blood was normal in all respects; red blood count 4.18, hemoglobin 77 per cent, white blood count 8,700, 66 per cent polymorphonuclears, 27 per cent leucocytes, 3 per cent large mononuclears, 3 per cent eosinophiles. On admission, nonprotein nitrogen was 35 mg. per cent; following sulfanilamide therapy it rose in three days to 58 mg. per cent; after sulfanilamide was discontinued, nonprotein nitrogen slowly fell and on discharge was 43 mg. per cent. Hinton and Kahn negative. Blood sulfanilamide level was 3.4. Sterile catheter specimens showed 0.4 gram-negative bacilli per field. Cultures were negative. Concentration dilution test: Patient concentrated between 1.004 and 1.010, diluted between 1.002 and 1.008. Urea clearance test: Clearance 45.2 per cent in the first specimen and 29.7 per cent in the second specimen. Phenolsulfonephthalein, at cystoscopy, in the right ureter there were 10 c.c. with less than 2.5 per cent phenolsulfonephthalein; left, 5 c.c., with less than 2.5 per cent phenolsulfonephthalein. Intravenous phenolsulfonephthalein, first specimen, 100 c.c., off color; second specimen, 90 c.c., 6 per cent; third specimen, 30 c.c., 1 per cent; fourth specimen, 95 c.c., 3.5 per cent. On cystoscopy, the bladder urine showed a slight trace of albumin, was alkaline, and showed 2 to 4 red blood cells per field. Right ureter showed albumin, 5 to 7 red blood cells per field in the sediment. Gram stain of urine from bladder, right and left ureters showed no bacteria.

X-rays.—Kidney, ureter, and bladder essentially negative. Retrograde bilateral pyelography showed no demonstrable abnormalities in the calices, pelvis, or ureters.

Clinical Course.—Concentration and dilution tests, urea clearance, and intravenous phenolsulfonephthalein were done. Following these the patient had a menstrual period. A later cystoscopy and pyelography were done. Bladder mucosa was dull. Extensive cystitis cystica over the trigone. Fourth phenolsulfonephthalein showed appearance time three and one-half minutes, both ureters. There was no residual. Following these studies, the patient was given 40 gr. of sulfanilamide, daily. On the third hospital day, the nonprotein nitrogen rose to 58 and sulfanilamide was discontinued and the nonprotein nitrogen began to decrease. Catheter specimen showed no bacteria. Culture was negative. Patient was discharged on the sixteenth hospital day, to be followed at the Boston Lying-in Hospital.

Grouped According to Blood Pressure Readings.—The blood pressure readings for this group are interesting. There were but 3 cases in which the blood pressure reached above 150/90 and those were the 3 patients who had a combination of

pyelonephritis and toxemia. Twelve patients showed blood pressure 120/or under. Three showed blood pressures below 100/000. These findings are particularly interesting, since these cases represent the most severe forms of pyelonephritis of the group studied. The low blood pressures were obtained in women who were ambulatory and living apparently normal lives.

Concentration Tests.—All of 17 patients (excluding the two patients who had died) concentrated their urines below 1.025, except 1 patient. That patient was a post-partum bilateral pyelonephritis case which still shows infection with *B. coli*. She was infected after her third and last pregnancy. Her intravenous phthalein test showed 0 per cent, 14 per cent, 28 per cent, and 22 per cent, for a total of 64 per cent in one hour after intravenous injection. She could hardly be considered to have normal kidneys.

Nonprotein Nitrogen Test.—All of 14 patients tested, except the living patient with toxemia were within the normal limits for nonprotein nitrogen readings. This patient with a reading of 40 mg. per 100 c.c. of whole blood could not be considered other than at the upper limit of normal.

Albumin.—Albumin was present, one-plus in 5 of 15 patients tested and three-plus in the eclamptic patient.

Wet-Stained Sediment Examination.—Pus was reported in 4 of 16 patients examined. Bacteria were noted in 5 patients as bacilli and in 1 as cocci. There was 1 patient in whom red blood cells were reported.

Stained Smear Preparations and Cultures.—Stained preparations in 16 patients showed 7 to be positive and all these were bacilli. Cultures were reported in 12 patients. Six patients were reported negative and 6 gave positive growths. Of the 6 positive growths, 5 were bacilli and 1 staphylococcus. There were 2 patients in whom small growths were thought to be contaminations and not to represent infection. Two patients showed different organisms in culture and stained smear preparations. Short bacilli grew out as cocci.

INTRAVENOUS PYELOGRAPHY, 10 CASES

Very poor, indistinct, inadequate filling	5
Normal pyelography, except for delayed filling	2
Poor outline of one kidney, that infected in pregnancy	1
Contracted kidney, that infected in pregnancy	1
Hydronephrosis, that infected in pregnancy	1

The best plate appeared about fifteen minutes after injection of the skiodan in 7 patients, at thirty minutes in 1, and the concentration of the dye was too weak to show outlines of pelves and calices in 2.

Intravenous Phenolsulfonephthalein Output.—In the 16 cases studied, the normal ratio of excretion of the dye, in which the initial fifteen-minute output reached at least 25 per cent, was present in but 3 of the 16 cases studied. All the remainder were below normal, or showed abnormal distribution of the dye among the four fifteen-minute periods, with a low initial output followed by increasing amounts of output in subsequent quarter-hour periods. This is indicative of delay in excretion. Three of the cases totaled less than 50 per cent for the hour of excretion. On the whole, the total excretion was not subnormal, but the chief abnormality was delay in output.

DISCUSSION

A summation of the data which have been presented indicates that particular attention should be paid both to parity and to whether the infection was ante partum or post partum, in estimating the probable severity of the patient's reaction to infection. As appears in the data here presented a definite relationship of these two factors to the degree of late damage which the patient will show after the lapse of years arows patients. In *Group I*, those which are characterized as mild can be established. Twenty of the 45 cases reported here are primip-

infections, but 5 of the 14 patients are primiparous. In the severe cases, 11 of the 19 cases occurred in primiparas. It has been stated (Crabtree, Prather and Prein³) that in multiple infected pregnancies the pyelonephritis which occurs in gestations subsequent to the initial infection is likely to be less severe, if febrile at all, than the initial infection.

It has been noted by many writers that the post-partum infections are less severe than ante-partum infections. In this series, 7, or 50 per cent, of the mild cases were post-partum infections, 3 were combined ante-partum and post-partum infections, and 4 ante partum. In the moderately severe cases, there were 6 ante-partum infections and an equal number of combined ante-partum and post-partum infections. In the severe cases, 9 cases were ante-partum, 7 were combined ante-partum and post-partum infections, making a total of more than 80 per cent of the group in which pyelonephritis during pregnancy was present and 2 patients showing only post-partum infection. If these figures are combined with the figures on parity, the conclusion is forced upon us that the most severe infections in association with pregnancy are in primiparas and in the ante-partum pyelonephritis.

No clean-cut evidence is produced here to indicate to what degree subsequent pregnancies increase the possibility of further damage to the kidneys of pregnant women. There seems to be evidence of voluntary limitation of further pregnancies among these women. Women who have suffered this disease cannot be blamed for reluctance to tempt fate a second time. Of the mild infections, 7, or 50 per cent, had no further pregnancies. Six of the 12 with moderately severe infections, also 50 per cent of the patients, had no further pregnancies, and 12 of 19 with severe infections had no subsequent pregnancies. Total figures indicate that 23 of the 45 patients with pyelonephritis had no further pregnancies. One patient had been sterilized, another died too soon for pregnancy to have taken place, leaving approximately one-half of the patients as a group in which pregnancy did not occur after the infected gestation.

Where pregnancy did take place subsequent to pyelonephritis, there is doubtful evidence of the significance of the following pregnancies in producing serious results, as noted in the body of the evidence from this series of patients. In 9 of the patients, there was 1 pregnancy which was apparently normal. Out of a total of 37 pregnancies which followed pyelonephritis, there was but 1 patient in whom there were toxemic symptoms, which developed in a patient who previously had not had toxemia. This fact seems to add weight to the point of view that toxemia and pyelonephritis are separate entities for the most part, with the possibility of occurrence of both in the same pregnancy, but with little else to link them together.

There is little evidence to indicate that the severity of the initial pyelonephritis is any criterion of the persistence of the infection beyond the average rate of spontaneous clearance. Of the mild cases, 5 of 14 patients were still infected at the time of final accounting. Of the moderately severe cases, 3 of 12 patients were known to have remained infected. Six of 19 patients with severe pyelonephritis were

known to have remained infected. In 5 patients, cystocele could have been a factor in retention of infection. In one of these, no upper urinary infection was shown.

Another point of view must be considered. It is generally accepted that pregnancy stasis is primary to pyelonephritis in pregnancy. In those cases in which, through ureteritis and subsequent scarring, hydro-ureter and hydronephrosis develop, reinfection could easily develop. In one patient in whom such a condition had taken place, reinfection has occurred three times in two years, after clearing of the infected urine had been accomplished by use of sulfanilamide. The urine was sterile to culture when tested at least a week after the withdrawal of the drug in each instance and remained clear for several months. This case is not one of the series. These residual infections are not more resistant to antiseptics than other lesions of the urinary tract unassociated with pregnancy.

Albuminuria.—Abnormal urines are the exception in these cases, if one excepts bacteriuria. In the one toxemic patient who is included in this series, there was found to be definite albuminuria with casts. There was no albuminuria in the 14 mild cases of pyelonephritis at the time of the re-examination. Albuminuria was found in one of the patients who had been classed as moderately severe infections, but in the group which had been classed as severe, 6 of the 15 patients studied showed albuminuria. Casts were not found in any of the pyelonephritis patients except the one who was toxemic in addition to pyelonephritic.

Pyuria.—In any consideration of urinary infection, two classifications of cases have always been made; i.e., bacteriurias and pyurias. The significance of these classes is not great. It is well recognized that the chronic stage of urinary infection is more nearly a bacteriuria and the still active stage of an infection is a pyuria. Often there is the difference of only a few hours between the two conditions in the same patient. At a given time, the determination of the amount of pus present is of some significance in determining the state of the infection, although this cannot be considered to represent constant findings at all times in the given patient. In quiescent infections, there are usually a few pus cells to be noted. We have here considered that 3 to 5 white cells to the high dry microscope lens field were average findings in quiescent infections. Where more cells than that were encountered, it was likely that the infectious process was still active. In the mild infections, there was 1 of the 14 patients who showed pus cells in excess of 3 to 5 per high power field. In the moderately severe cases, 2 of 9 patients examined showed pus, and in those who had been severe, 4 of 16 patients showed pus.

Total Renal Deficiency in Unilateral Infections.—Thirty-one of the 45 patients studied had cystoscopic study at the time of the initial pyelonephritis. Unless there had been extensive studies, including cultures taken under adequate precautions, made at the time of the original pyelonephritis, one could not say with certainty that some of these cases were unilateral. In some, the unilateral nature of the original infection was established, but in many it was not. In the other patients, however, there was absence of symptoms, clear ureteral urines, absence of bacteria on stained preparations from the ureteral catheter urines, and absence of pus. If infection of the supposedly normal other side took place through cystoscopy, it produced no symptoms. Six of the 12 patients with mild cases were cystoscoped, 10 with moderately severe cases, and, as one would expect in that stage of management of pyelonephritis patients previous to present anti-sepsis, 15 of 19 patients with severe cases were cystoscoped. There were 11 unilateral infections. One of these was a congenital absence of one kidney, and one had insufficient data to establish its nature. Of the 11 patients, 4 were entirely normal to all tests at the time of this study. Seven showed renal

deficiency in some or all of the tests performed. It is of interest, furthermore; that it seemed to make little difference whether one or both kidneys were involved in the initial pyelonephritis for classification of the cases as mild, moderately severe, or severe cases. It was noteworthy, also, that it was of little significance whether there had been unilateral or bilateral initial infection, since total renal deficiency was encountered in both instances. There were no data except the history of the patients to indicate whether infections subsequent to the original pyelonephritis had intervened. History of such occurrence was seldom encountered. In this respect one should note Volhard's⁴ statement that excretion of indigo carmine by one healthy kidney may be severely impaired by some reflex action or toxic substance from the diseased opposite kidney and may be found normal after surgical removal of the diseased kidney. There are a few clinical reports in urologic literature of such occurrences. One of us (E. G. C.) has one instance of this condition which occurred in a man; accompanied by high nonprotein nitrogen retention, which continued to rise several days after nephrectomy was done, eventually returned to normal findings, but later became abnormal again after some months.

Phenolsulfonephthalein Test.—Abnormal delay in excretion of phenolsulphonephthalein with ability to concentrate the urine was the most constant abnormality encountered in these cases. The total output of the drug was seldom lower than normal. There was a constant finding in most cases that the first fifteen-minute

TABLE I

PHENOLSULFONEPHTHALEIN					NONPROTEIN NITROGEN	CONCENTRA- TION
15"	30"	45"	60"	TOTAL PER CENT		
26	16	15	7	64	29	1.020
0	14	28	22	64	31	1.028
33	18	10	12	73	32	1.014
10	13	9	7	39	40	1.016
30	22	25	15	92	30	1.017
15	25	12	10	62	25	1.020
18	12	12	6	48	27	1.017
18	18	10	5	51		1.015
1	35	16	9	61	26	1.023
10	20	30	10	70	25	1.023
35	23	13	7	78	35	1.023
25	17	25	10	77	29	1.017
13	20	28	23	84	27	1.016
25	14	18	15	73	26	1.018
27	18	10	30	65	31	1.022
10	15	35	10	70	30	1.020
30	23	10	5	68	25	1.021
20	30	25	8	83	30	1.020
38	32	12	10	92	28	1.025
30	20	17	10	77	28	1.027
40	23	13	6	82	33	1.026
40	17	13	9	79	28	1.018
40	30	10	8	88	33	1.021
50	25	10	7	92	29	1.023
30	18	15	7	71	28	1.026
16	25	38	7	86	28	1.026
14	32	23	10	79	28	1.026
15	28	20	8	71	33	1.022
25	25	20	15	85	36	1.022
10	20	25	20	75	33	1.024
14	25	15	17	71	31	1.022
15	23	14	5	57	28	1.018
16	30	20	8	74	31	1.022
18	13	30	15	76		1.012
15	15	10	5	45		

output was below normal, but that the output in subsequent excretion periods was more satisfactory. The result was a flattened curve of excretion for the group as a whole, as shown in Fig. 1. The data for the 37 patients from whom this figure was obtained are appended in the chart with the nonprotein nitrogen test and the concentration of the urine test.

Nonprotein Nitrogen Test.—There was no evidence of retained nitrogen, as indicated by the estimation of nonprotein nitrogen in 34 cases, except in the one eclamptic patient.

Concentration Test.—It was evident from a study of the data on ability of these patients to concentrate their urines to 1.025 or higher that this test was most likely to show deficiency in the severe cases. Of the total 34 patients tested, 27 failed to concentrate to 1.025. In the group of mild cases, 3 patients concentrated to 1.025 or above. Eleven of the 14 patients were under 1.025. In the moderately severe group, 3 of 8 patients tested were below 1.025, but all were above 1.020. In the severe group, 16 of the 17 patients tested were below 1.025. In all three groups, there were but 7 patients in whom the concentration reached 1.025 or above; 15 concentrated to 1.020 or under; and 3 concentrated to 1.015 or under. The lowest figure was in an uninfected, nontoxemic patient, who concentrated to 1.012.

Hypertension.—Blood pressure readings in excess of 150/90 were found to be present in 9 of these patients. Three of the patients were definitely toxemic in addition to the infections. Six of 42 patients with pyelonephritis showed hypertension five to ten years after the initial infection occurred. Three of these hypertension occurred in the patients with mild cases and 3 of them with severe cases.

In estimating the normal blood pressure readings for any group, one must consider many factors. We have preferred to accept the averages for the age groups for women as established by Weatherby.⁵ He assigns a mean systolic pressure for the age group 30 to 39 of 125.83, with probable error plus or minus 0.48, a standard deviation of 19.79 with probable error plus or minus 0.34, and coefficient of variability 15.73. Since the average childbearing age is about 25, these patients should be expected to fall, and do fall, into the age group 30 to 39 years at the time of re-examination.

Intravenous Pyelography.—Twenty-one of the whole group of study cases had intravenous pyelography. The films were examined for evidence (1) of delayed excretion of the dye; (2) of either acquired or pre-existing abnormalities of the conducting channels, pelvis and ureter; (3) of contracture of the cortex; and (4) concretions.

Six of the 21 cases showed prompt filling of the pelvis and ureters early within the first fifteen-minute period after injection of the dye. Nine cases showed the best filling at fifteen minutes, and 2 cases showed best filling at thirty minutes after injection of the dye. In 4 cases, there was such poor filling that the outlines of pelvis and ureters were never satisfactorily demonstrated during the course of the examination. Two of the latter cases occurred in the mild and 2 in the severe group.

Five patients showed irregular small calices which were suggestive of contracture of the cortex. Four of these were in the mild group and 1 in the severe group. Four patients showed inflammatory changes in the conducting channels. In 1 there was, in addition, a lesion which suggested aberrant vessel which must have antedated the pregnancy injury.

Stone was present in 5 patients. These calculi were all small in the 3 cases which we demonstrated but, in addition, 2 patients had been operated upon elsewhere for renal calculus. This incidence is far above the normal incidence for a stone in women.

CONCLUSIONS

1. In a survey of 45 patients with pyelonephritis associated with pregnancy, evidence was produced through examination by intravenous pyelography, intravenous phenolsulfonephthalein excretion,

concentration of the urine test, and tests for retention of nitrogen, to indicate that a high percentage of patients suffer appreciable damage to their kidneys which is demonstrable at from five to ten years after the infection. For the majority, adequate renal function is present at that time.

2. In the patient in whom there has been both toxemic and pyelonephritic injury, the prognosis is grave. Hypertension was found to be present in all the patients where there had been both toxemic and pyelonephritis (3 cases). Two of the 3 were dead at 5 years after the injury.

3. Six patients with pyelonephritis showed blood pressure readings above 150/90, associated with some evidence of renal deficiency at that stage of the natural history of the disease.

4. Renal injury, as demonstrated in this group, consisted of injury both to the conduction channels, pelvis and ureter, and to the cortex. When there is injury to the conducting channels, the stasis of urine produced by this condition may further injure the cortex, especially when infection is still present. Stone occurred in 5 of the 45 patients studied.

5. Evidence of total renal deficiency was present at the time of examination in some proved unilateral cases. This finding suggested some other injury than bacterial invasion for the second kidney.

6. It is our impression that the pyelonephritis of pregnancy should be looked upon as a progressive disease in many cases. Data have not yet been produced to indicate to what extent it shortens life. Some of the cases which were subnormal may have shown only the original damage and may now be in a stationary state.

7. Sufficient evidence has been produced to indicate that the aim in treatment in pyelonephritis associated with pregnancy should be to minimize the initial injury and clear the infection as soon as possible.

REFERENCES

- (1) *Peters, J. P.*: J. A. M. A. 110: 329, 1938. (2) *Hage, W.*: Ztschr. f. urol. Chir. u. Gynäk. 44: 172, 1938. (3) *Crabtree, E. G., Prather, G. C., and Prien, E. L.*: AM. J. OBST. & GYNEC. 34: 405, 1937. (4) *Volhard, F.*: In Berglund: The Kidney in Health and Disease, Philadelphia, 1935, Lea & Febiger, p. 245. (5) *Weatherby, M.*: In Berglund: The Kidney in Health and Disease, Philadelphia, 1935, Lea & Febiger, p. 374.

ERYTHROBLASTOSIS FETALIS*

WITH A REPORT OF TWENTY-SEVEN CASES

SAMUEL A. WOLFE, M.D., F.A.C.S., AND IRWIN NEIGUS, M.S., M.D.,
BROOKLYN, N. Y.

(From the Departments of Obstetrics and Gynecology, Brooklyn Jewish Hospital)

ERYTHROBLASTOSIS fetalis designates a disease of the blood-forming organs of the newborn and neonatal infant characterized by anemia and by the presence of an excessive number of immature red blood cells in the circulation. The English hematologists view the disease as a primary hemolytic anemia, the immature red cells resulting from accelerated compensatory regeneration. The American concept advanced by Diamond, Blackfan and Baty entertains a primary overgrowth of immature red cells which undergo rapid hemolysis. Generically, the disease embraces hydrops fetalis, icterus gravis neonatorum, and anemia hemolytica neonatorum.

Ballantine collected 70 cases of hydrops fetalis described in the literature between the years 1614 and 1898. Schridde, in 1910, first recognized the pathology in the hematopoietic organs of infants with hydrops. In 1910, Bachan and Comsie emphasized the presence of large numbers of nucleated red cells in the blood, and the persisting hematopoietic foci in the liver and spleen of infants with icterus gravis. Priority for the description of congenital anemia is accredited to Ecklin whose article appeared in 1919. More recently De Lange, Ferguson, Diamond, Blackfan and Baty, and also Hellman and Hertig, have made illuminating contributions.

HYDROPS FETALIS

Fetal erythroblastosis appears once in every 1,200 to 2,000 confinements. In Stander's clinic, it was encountered once in every 4,000 births and was considered the cause of death in 4.5 per cent of all still-born infants over 1,500 Gm. A recent article by Macklin records two stillborn infants with normal external appearances in whom autopsy revealed erythroblastosis. The actual frequency of the disease may therefore be greater than recorded. An incidence of 1:2,000 is reported for hydrops fetalis by Hellman and Hertig. Between Jan. 1, 1933 and July 1, 1939, 4 cases of hydrops fetalis occurred in 15,334 confinements at the Brooklyn Jewish Hospital, an incidence of 1 in 3,833 deliveries.

The etiology of erythroblastosis is unknown. In hydrops, as in the other clinical types, a definite racial predisposition is emphasized in the literature. Mediterranean people are especially prone to this illness. In our 4 cases of hydrops, however, one mother was an American-born white, one of American colored stock, and two were of Russian-Jewish extraction. A high familial incidence has been shown by Fanconi

*Read at a meeting of the Brooklyn Gynecological Society, October 6, 1939.

in a study of 22 families in which erythroblastotic children were born. In Hellman and Hertig's series, the disease was repeatedly noted in 7 of 20 families investigated. The first and last children are generally free from the disease or display only mild manifestations. Nulliparas are rarely affected. An average parity of 5.2 is noted by Hellman and Hertig, who also add that when erythroblastosis appears in any form, there is a 50 per cent chance that the succeeding sibling will present hydrops fetalis. Of 4 mothers in our series who delivered infants with hydrops fetalis, 3 previously delivered stillborn children. The average age was 25.2 and the average parity in our series was 2. Two mothers followed in succeeding pregnancies were delivered of normal children (Cases 2 and 3).

Clinically, hydrops fetalis is the most severe form of erythroblastosis. A stillborn infant or death after feeble respiration is the rule. The longest life period recorded is six days. The infant presents a waxy skin with multiple zones of cutaneous hemorrhage. Edema is marked.

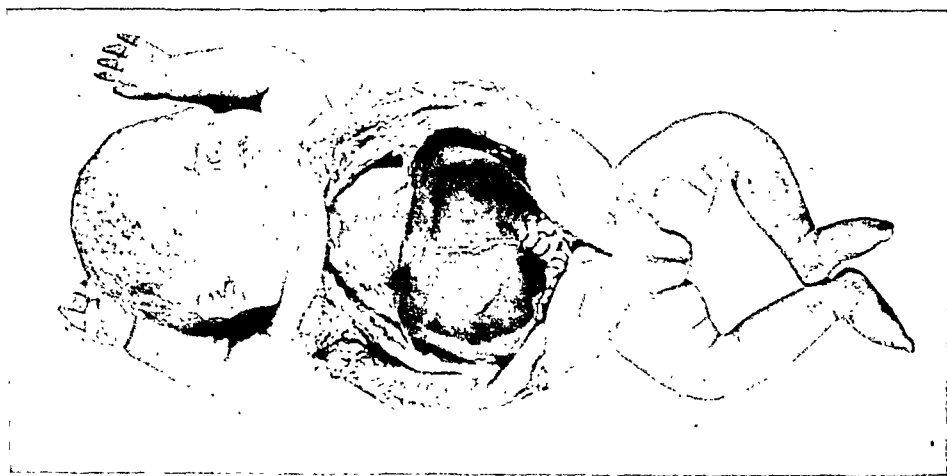


Fig. 1.—Fetus in the hydropic type of erythroblastosis. The superficial tissues are swollen and waxy. Hemorrhagic areas are noted on the face. The huge liver fills the abdominal cavity and contributes to its enlargement.

Jaundice is occasionally noted. The face is enlarged and swollen, the neck short, and the abdomen markedly distended. The latter results from the presence of free fluid in the abdominal cavity and enlargement of the liver and spleen which are felt for varying distances below the costal arch (Fig. 1).

Pathologically, the skin presents marked subcutaneous edema. Petechial hemorrhages are noted in the external and internal organs. The pleural cavity often contains excess fluid. The heart is enlarged, and its weight definitely increased. The abdominal cavity holds a varied quantity of serosanguineous fluid. The liver reaches from two to five times its normal dimensions and is reddish brown and glistening. On cut section its lobular structure is somewhat obscured. Microscopically, zones of toxic necrosis and deposition of iron or bile pigment are encountered. Hematopoiesis is pronounced. The sinusoids are distended and contain numerous premature cells of the red cell series (megalo-blasts, erythroblasts, and normoblasts). The white cell group is repre-

sented by the myeloblast and myelocyte (Fig. 2). The portal canals are filled with similar cells. The spleen is enlarged, soft, and reaches four to five times its normal size and weight. It is generally firm in consistency and red brown in color. Malpighian corpuscles are not reproduced. The pulp is filled with hordes of immature nucleated red cells and large progenitors of the white cell series. Pigment-laden phagocytes are numerous. The pancreas, adrenals, kidneys, prostate, thymus and pituitary share in the extramedullary proliferation of immature blood cells. The bone marrow is hyperplastic and compactly filled with proliferating erythroblastic and myeloblastic cells, the former largely predominating. The placental changes are noteworthy. The organ is enlarged, soft, and friable. Its maternal aspect is deeply fissured. The yellow gray color is striking. The fetal placental weight ratio is altered

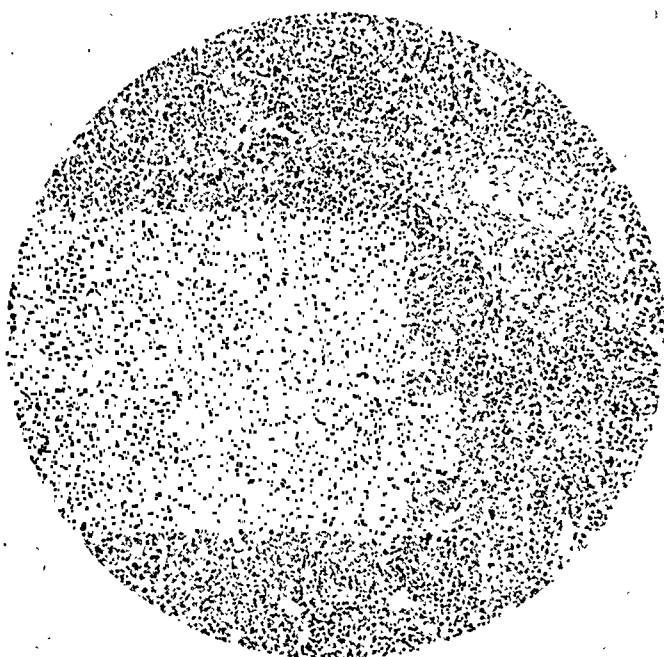


Fig. 2.—Liver in erythroblastosis fetalis. The liver cords are widely separated. The sinusoids are filled with large numbers of immature red blood cells. Immature white cells can also be identified. The portal canals also show persistent hematopoiesis. $\times 150$.

from the normal of 6:1 and can reach an extreme of 3:1. Edema of the organ is the accounting factor. Microscopically, the villi are large and even in premature placentas reach beyond the normal size. The syncytial cells are regularly spaced. Syncytial buds are frequent. The Langhans layer may focally persist. The stroma is edematous but hyperplasia may be pronounced. Hofbauer cells normally present only in the early placenta are encountered with moderate frequency. The capillaries are reduced in number and contain numerous red and white blood cells (Fig. 3).

The hematologic changes in this lesion are diagnostic and will be more fully discussed under icterus gravis. Reduction in the number of red cells is outstanding. The hemoglobin, too, is low but the color

index is above the normal. The number of nucleated cells, which in the neonatal period range from 20 to 25,000, is markedly increased. The rise in the number of nucleated red blood cells is especially pronounced, and normoblasts sharply increase above 15 per cent, the high normal figure for the neonatal period. Erythroblasts, megaloblasts, myeloblasts and myelocytes are found on smear. Studies of the blood picture in hydrops cases, as a rule, are incomplete or entirely omitted because of the early death of the infant. In our series only three infants had partial blood studies, all made post mortem. One showed 78 normoblasts per 100 white blood cells (Case 2). One showed 149 normoblasts for every 50 cells of the white cell group (Case 4). Case 1 studied by post-mortem sternal puncture showed a marked increase in the ratio of early red cells.

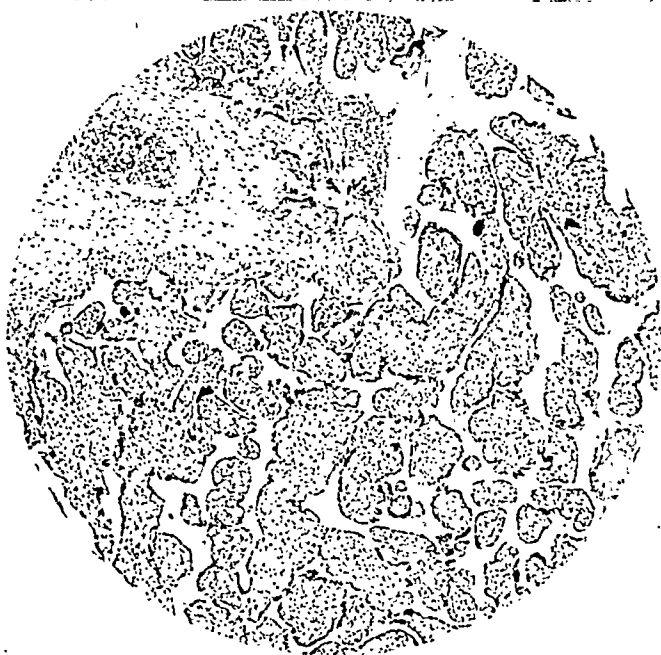


Fig. 3.—Placenta. The large size of the villi is prominent. Note the immature mesenchymal stroma. Hofbauer cells are not infrequent. The syncytium is vesicular. Large numbers of syncytial buds are prominent. Note the large numbers of nucleated red cells in the vein of a main stem villus. $\times 80$.

Pregnancy associated with hydrops fetalis is frequently accompanied by hydramnion. This may explain the increased incidence of premature labor. Of 4 patients, one was delivered in the thirty-fourth week, one in the thirty-sixth week, one in the thirty-seventh week, and one in the thirty-eighth week. The incidence of toxemia of pregnancy is above the normal. In the series reported by Hellman and Hertig, it was encountered in 30 per cent of the patients. In our group, 2 of the 4 patients showed moderate toxemia evidenced by edema, moderate rise of blood pressure and albuminuria. Maternal blood studies are not recorded with sufficient frequency to determine any correlation between fetal and maternal hematopoietic abnormalities.

Labor may be complicated. In 2 of our 4 patients (Cases 3 and 4), fetal dystocia resulted from the enlarged abdomen. In Case 3, it delayed delivery after internal version was performed for prolapse of the cord. Abdominal paracentesis and partial evisceration were necessary to complete the delivery of Case 4. The third stage as a rule follows without incident, in spite of the huge size and weight of the placenta.

The diagnosis of hydrops fetalis is easily established at birth by the clinical appearance of the infant, and confirmed by study of smears made from cord blood. Even before delivery, an amber colored amniotic fluid directs suspicion. Intrauterine diagnosis can be made by x-ray as first shown by Hellman and Irving. In the roentgenogram, the subcutaneous tissues are definitely thickened and show marked density. A corona surrounds the bones of the skull due to marked edema of the scalp. Congenital syphilis must be excluded, for like erythroblastosis it too may affect successive infants causing death in utero or early in the post-partum period. Enlargement of the liver, spleen, and placenta completes the parallel between syphilitic and erythroblastic infants. X-ray studies of the long bones for osteochondritis, microscopic examination of the placenta, serologic examination and smear of the cord blood clarify the situation.

The prognosis of hydrops fetalis is bad. Survival of the infant is practically unknown. Because of the tendency of recurrence in succeeding pregnancies, advisability of future childbearing must be strongly considered. There is no effective treatment. Liver and vitamins have been administered to mothers as prophylactic measures.

CASE REPORTS OF HYDROPS FETALIS

CASE 1.—Mrs. E. B. (No. AA43210), para ii, aged 28 years, Russian Jewess, was admitted Jan. 15, 1938, because of suspected nephritic toxemia. The first pregnancy in 1933 was uneventful. The second pregnancy in 1935 resulted in the birth of a premature stillborn infant at 7½ months. The present pregnancy dates from June 25, 1937, and was uneventful until Jan. 11, 1938, when edema and elevation of blood pressure appeared. There was no response to medical treatment. On admission the physical examination was essentially negative. The uterus measured 23 cm. Fetal presentation was L.S.A. and the fetal heart normal. The pelvic measurements were ample. Bilateral edema of the fingers and legs was noted. The blood pressure was 164/76. The urine showed 4-plus albumin with moderate numbers of casts and occasional red blood cells. The Kahn and Wassermann reactions were negative. The blood studies revealed mild secondary anemia. Labor occurred prematurely on Feb. 22, 1938, and resulted in the birth of a stillborn breech infant which weighed 3,300 Gm. The edematous placenta, weighing 1,680 Gm., was delivered spontaneously five minutes later. The post-partum course was uneventful. Autopsy revealed a female infant 41 cm. in length and weighing approximately 3,178 Gm. The skin was edematous and contained numerous zones of hemorrhage. The abdomen was especially protuberant and measured 40 cm. in circumference. Upon incision 600 c.c. of clear straw-colored fluid was evacuated. The lungs were collapsed. The heart was enlarged and measured 4 cm. from apex to base and 4 cm. transversely across the base. The weight was 22 Gm. The atria were dilated. The valves, chordae tendinae, papillary muscles, and ventricular walls showed no abnormalities. The ductus arteriosus and the foramen ovale were patent. The gastrointestinal tract presented no pertinent findings. The liver reached 6 cm. below the costal arch and the dome of the diaphragm was definitely elevated. It measured 13 by 9 by 4 cm. and weighed 183 Gm. (normal 78 Gm.). The external surface was smooth,

shiny and red brown. On cut section the markings were indistinct. Microscopically, the arrangement of the lobules was fairly well preserved. The central veins, however, were dilated and contained numerous nucleated red blood cells. The dilated sinusoids were compactly filled with huge numbers of early red and white cells. The portal canals similarly contained young white and red blood derivatives. The pancreas was normal. The suprarenal glands presented no abnormalities but the medullary segments contained foci of hematopoiesis. The blood vessels were crowded with normoblasts, megaloblasts, and myeloblasts. Similar areas of hematopoiesis were noted in the cortical and medullary segments of the kidneys. The genitalia were normal. The spleen was enlarged and weighed 32 Gm. (normal 8 Gm.). It measured 7 by 5 by 4.2 cm. The external surface was smooth, the color brown purple. On cut section the Malpighian corpuseles were indistinct. Microscopically, the sinusoids and the pulp were crowded with huge numbers of early red and white cells. The bone marrow as studied in the ribs, vertebrae, and tibia showed marked hyperplasia and the

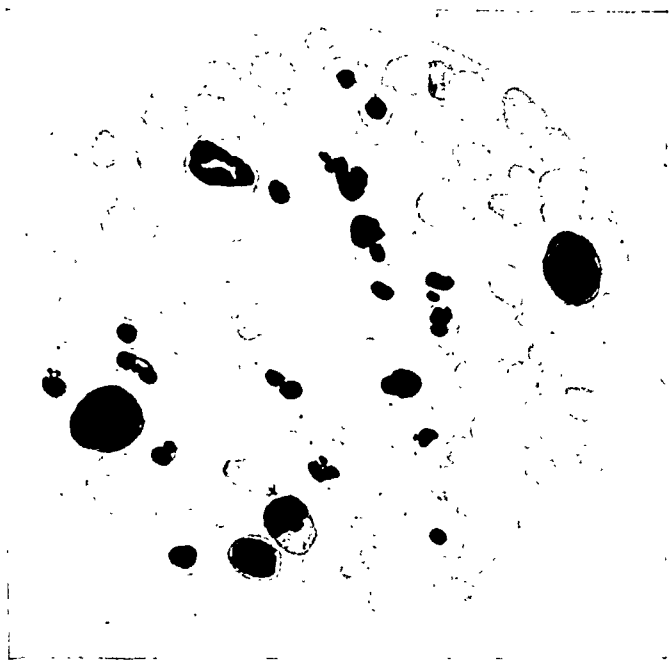


Fig. 4.—Photographed drawing of smear from sternal bone marrow puncture. Note the erythroblasts in the upper portion. Normoblasts are numerous. The large, deeply-staining, round cells are megaloblasts.

marrow spaces were packed with nucleated red cells, early white cells, and occasional megakaryocytes. A post-mortem sternal puncture showed a ratio of 5 white cells to 95 erythroblasts (normal ratio 95:15; Fig. 4). The ratio of early red cells to matured red cells was 40:60 (normal ratio 15:85). The cranial cavity showed clotted blood in the middle and posterior fossae. The falx and tentorium were normal. The brain weighed 182 Gm. and presented no abnormalities. The edematous placenta weighed 1,680 Gm. and measured 24 by 13 by 3 cm. The maternal aspect was deeply fissured. Microscopically, the chorionic villi were larger than normal and the syncytial cells were somewhat flattened. Langhans' cells were focally retained. The connective tissue stroma was vacuolated and Hofbauer cells encountered with moderate frequency. Syncytial giant cells were numerous.

CASE 2.—Mrs. E. G. (No. AA29066), primipara, aged 23 years, American-born, was admitted in labor Oct. 6, 1933. The last menstrual period occurred Jan. 11, 1933, and the estimated date of confinement was Oct. 18, 1933. Labor terminated prematurely at the thirty-seventh week. The child lived only forty-five minutes.

Autopsy revealed a female infant with striking subcutaneous edema of the skin and mucous membranes. The abdomen was distended. The peritoneum and pleural cavities contained an excessive amount of straw-colored fluid. The heart weighed 20 Gm.; the myocardium was pale and edematous. The liver weighed 115 Gm. and was red, smooth, and glistening. Microscopic examination revealed numerous islands of hematopoiesis in the sinusoids and in the portal canals. The spleen was enlarged and weighed 33 Gm. Its surface was smooth and red. Microscopic examination revealed the stroma and sinusoids filled with numerous immature cells, many of which were megaloblasts. There were foci of hematopoiesis in the skin, intestine, kidney, uterus, pancreas, and adrenals. The ribs and long bones contained a deep red marrow which showed marked erythroblastic activity. The post-mortem blood smear revealed 78 normoblasts per 100 white cells and 17 megaloblasts per 100 white cells. The differential count revealed 69 per cent lymphocytes, 14 per cent polymorphonuclear cells, 6 per cent band forms, 3 per cent eosinophiles, and 7 per cent myeloblasts. The placenta was not studied. A subsequent confinement on Dec. 8, 1937 resulted in the birth of a normal, full-term male infant which weighed 3,486 Gm.

CASE 3.—Mrs. R. S. (No. AA2453), para i, aged 26 years, Russian Jewess, was admitted in labor Oct. 7, 1934. The first pregnancy in 1932 terminated in the birth of a full-term stillborn infant. The last menstrual period occurred Jan. 18, 1934, and the estimated date of confinement was Oct. 25, 1934. On admission there was slight edema of the extremities and polyhydramnion. With full dilatation, artificial rupture of the membranes was followed by the prolapse of the cord. Delay in delivery of the child after podalic version was due to the enlarged abdomen and resulted in a stillborn male infant, weighing 4,131 Gm. The edematous placenta followed spontaneously. At autopsy, the skin was markedly edematous, the abdomen greatly distended, containing 300 c.c. of amber-colored fluid. Each of the pleural cavities contained 75 c.c. of yellowish red liquid. The heart was enlarged, weighed 30 Gm. and showed dilatation of the atria. The lungs were collapsed. The liver weighed 159 Gm., the surface was smooth and the consistency firm. The spleen was also enlarged, weighing 30 Gm. and was covered by a fibrinous exudate. Microscopic examination of the organs showed numerous areas of hematopoiesis in the liver, spleen, kidneys, and adrenals. The placenta weighed 1,930 Gm. and presented the classical pale, soft, fissured appearance. The villi showed marked edema, and the capillaries were filled with numerous nucleated red blood cells. The succeeding confinement in December, 1936, resulted in the birth of a normal, full-term male child, weighing 3,968 Gm.

CASE 4.—Mrs. J. B. (No. 209438), para ii, colored, born in the United States, was admitted in labor on Feb. 17, 1938. The first pregnancy in 1936 resulted in a stillborn infant at seven and one-half months. The last menstrual period occurred July 1, 1937, and the estimated date of confinement was April 8, 1938. The Wassermann test was positive and the patient received eight injections of salvarsan during her ante-partum course. On admission the blood pressure was elevated to 150/98. Fetal dystocia resulted from the markedly enlarged abdomen. Paracentesis, accordingly performed, was followed by a large gush of fluid, after which the dead male infant was easily delivered. The placenta followed spontaneously. The smear from the cord blood immediately studied showed 149 normoblasts for every 50 white blood cells. Autopsy revealed a colored male child 43 cm. in length and weighing 2,050 Gm. The heart weighed 15 Gm. and was otherwise normal. The liver weighed 78 Gm. (enlarged for premature). Its surface was smooth, glistening, and deep red. Microscopic examination revealed numerous foci of hematopoiesis. The central veins, sinusoids, and portal canals were filled with numerous normoblasts and megaloblasts. There were no miliary gummas and spirochetes were not demonstrated. The spleen, kidneys, and adrenals showed numerous zones of hematopoiesis. The bone marrow was packed with immature red and white cells. The soft friable placenta weighed 915 Gm. (ratio 2:1). Microscopic examination revealed enlarged chorionic villi with vacuolated stroma and occasional Hofbauer cells. The fetal veins and capillaries contained large numbers of normoblasts and occasional erythroblasts and myeloblasts.

ICTERUS GRAVIS NEONATORUM

Icterus gravis neonatorum designates that clinical form of erythroblastosis, in which jaundice is the most prominent symptom. Edema is supposedly lacking, but in our series are included five infants presenting circumscribed swelling of the subcutaneous tissues. As will be noted below, these cases were severe and clinically are perhaps considered as intermediary between hydrops and icterus gravis.

Icterus gravis is not infrequent. Hellman and Hertig report an incidence of 1 in every 1,500 confinements. In our survey from Jan. 1, 1933, to July 1, 1939, 20 cases of icterus neonatorum were encountered in 15,334 deliveries, an incidence of 1 in every 767 confinements. The etiology is unknown. Mediterranean ancestry is emphasized as a predisposing cause, but in our series of 19 mothers who delivered 20 icteric infants, 12 were born in the United States, 2 in Austria, 2 in Russia, 1 in Germany, 1 in Italy, and 1 in Rumania. There were no patients of the colored race. Multiparas predominate and in our series the average parity was 2.7; the average age was 31.2 years. Recurrence of the disease in succeeding pregnancies is frequent. Hellman and Hertig indicate that once erythroblastosis has appeared there is an 80.3 per cent chance that the succeeding child will present icterus gravis. Of our 19 mothers, 4 delivered stillborn infants in earlier pregnancies. Four others had previous erythroblastotic children. Infants 1 and 2 were succeeding icteric children from the same mother. In Case 3, hydrops fetalis and 3 other stillbirths anteceded the birth of the icteric infant. In Case 6, the second infant presented congenital anemia and the third, icterus gravis. In Case 18, the first pregnancy was a full-term stillbirth; the second child succumbed to icterus gravis. The third and fourth pregnancies of this mother terminated in premature stillborn children at six and eight months, respectively. Two mothers who delivered icteric children were followed in succeeding pregnancies. The mother of Case 1 delivered a second icteric child. In Case 20, the succeeding pregnancy terminated in a premature stillborn infant, evidently due to strangulation of the cord.

The most prominent symptom of icterus gravis is jaundice which may be present at birth or be delayed for twenty-four to forty-eight hours after delivery. A saffron yellow vernix caseosa arouses suspicion. In our series 6 infants were jaundiced at birth. In 3, icterus appeared within eight hours; in 5, between eight and twenty-four hours; and in the remaining 6, within twenty-four to forty-eight hours after delivery. The infants are generally listless, apathetic and feed poorly. As the disease progresses, stupor and convulsions appear. In the terminal stages, vomiting, dyspnea, cyanosis, and frothing of blood-stained fluid are frequent manifestations. Cutaneous hemorrhage is not uncommon. Though jaundice may be intense, the mucous membranes are not uncommonly pallid. Enlargement of the liver and spleen affords palpation of these organs for varying distances below the costal margin.

The pathologic changes are essentially similar to those encountered in hydrops. Diffuse edema, however, is lacking although circumscribed swelling was noted in five infants. The skin, as the other fetal tissues, presents icterus of varying degree. The heart is enlarged and its chambers dilated. The size, however, is somewhat smaller than noted in hydrops. The peritoneal cavity contains small amounts of fluid. The liver is increased two to five times its normal dimensions. The weight is augmented. The color is greenish brown. On cut section the sinusoidal markings are poorly defined. Microscopically, the dilated sinusoids are compactly filled with nucleated red cells and the early large progenitors of the white cell group. Numerous foci of hematopoiesis are present. The liver cords are compressed and the liver cells contain bile pigment and hemosiderin. The portal canals show persistent hematopoiesis. The spleen is similarly enlarged from two to five times its normal dimension and generally presents a purple red color. The Malpighian corpuscles are not reproduced. The pulp shows numerous foci of erythropoiesis. Pigment laden endothelial phagocytes are frequent. Other organs, too, show extramedullary blood formation but seemingly with less fre-

quency than in the hydrops group. The bone marrow is hyperplastic and is compactly filled with huge numbers of early red blood cells. The brain may present a striking appearance. The basal ganglia (thalamus, corpus striatum, caudate nucleus, olivary bodies, vermis, and the floor of the fourth ventricle) take a yellow, yellow green, or olive stain; so-called "Kern-icterus." Microscopically, the brain cells in these areas contain yellow pigment granules in the body cytoplasm. This was encountered at autopsy in four cases (7, 12, 16, 19). The placenta is generally normal in its gross appearance. Microscopically, there are a few departures from the normal. The Langhans layer is occasionally retained. Hofbauer cells are noted. The diagnosis, however, is generally established by the finding of excessive numbers of nucleated red blood cells in the capillaries of the villi.

The hematologic findings reveal a hyperchromic anemia. The red cells average 3.4 million compared to a normal of 5.2 to 5.6 million for the neonatal period. The hemoglobin is reduced and averages about 51 per cent. The color index is high. Nucleated cells range from 23,000 to 256,000. The normal is 20,000 to 25,000 for this period. Fifty per cent to 90 per cent of the nucleated cells belong to the red cell type, contrasting with the average normal of 5 to 15 per cent for the neonatal period. The bleeding time is prolonged, the clotting time is normal. The icteric index is markedly elevated. Fragility of the red blood cells shows no departure from the normal. In our series the hemoglobin varied from 50 to 160 per cent. The red blood cells ranged from 1.43 to 6.75 million per c.mm. Polycythemia occurred in 4 cases (1, 4, 8, 11). Nucleated red cells varied from 7 to 300 per cent with an average of 69 per cent.

Pregnancy associated with icterus gravis shows a greater incidence of toxemia. Hellman and Hertig report two mild cases in 19 mothers. Mild toxemia was observed in Cases 1, 4, 5, and 8 of our series. Labor, as a rule, is frequently premature. Nine of our 20 infants were delivered prematurely; 2 in the thirty-fourth week, 1 in the thirty-fifth week, 3 in the thirty-sixth week, 1 in the thirty-seventh week, and 2 in the thirty-eighth week. Labor was of normal duration and averaged 11.3 hours for our series. The weight of the children ranged from 2,300 to 3,996 Gm. The average weight was 2,948 Gm. Blood studies on mothers were not made with sufficient frequency to warrant any statement.

The diagnosis of icterus gravis is easily made. Jaundice, an enlarged liver and spleen and an increased number of nucleated red cells form a diagnostic triad. A golden yellow vernix if present at birth is indicative of the illness. Icterus gravis should be anticipated in a mother presenting a history of repeatedly stillborn infants without apparent cause or where a history of previous erythroblastosis is obtained.

The illness is grave and the fetal mortality as reported in the literature reaches from 50 to 80 per cent. Infants with icterus at birth receiving prompt and adequate treatment show a better prognosis. Of 7 infants with icterus at birth, 3 were recognized and prompt treatment resulted in recovery. Three others died without therapy because the lesion was not diagnosed. The fourth infant succumbed in spite of transfusion because of concomitant cerebral hemorrhage. Of 7 in whom jaundice appeared within twenty-four hours, 1 recovered and 6 died. Of the remaining 6 infants displaying icterus between twenty-four and forty-eight hours after birth, 5 succumbed. Six of the fatal cases presented 85 per cent or more normoblasts on examination of the blood smear. Of these, 1 died in fifteen hours, 3 within thirty-one hours, 1 in sixty hours, and 1 in sixty-six hours. Cases with circumscribed edema were severe and in our series all died. Recovery may be followed by a phase of anemia. Cirrhosis of the liver and neurologic lesions are on record as sequelae.

As in the therapy of hydrops fetalis, liver, iron, and vitamins have been advised as prophylactic measures for mothers who have previously delivered erythroblastotic children. Treatment of the icteric infant should be prompt and immediate for the prognosis frequently depends upon early and adequate measures. Intramuscular injections of human blood serum or whole blood have been employed with varying results. Five to 15 c.c. of serum are administered daily for a total of 30 to 60 c.c. Hampson reports 17 recoveries in a group of 18 icteric infants

TABLE I. MATERNAL FINDINGS IN ICTERUS GRAVIS

CASE	AGE	PAR-ITY	NATION-ALITY	PRE-VIOUS STILL-BIRTHS CAUSE UN-KNOWN	PREVIOUS ERYTHRO-BLASTOSIS	MILD TOX-EMIA	LABOR			POST PARTUM	SUBSE-QUENT PREG-NANCIES
							WEEK	DURA-TION (HR.)	TERMINA-TION		
1	27	i	Am.-Jewess	0	0	+	36	8	Spont.	Normal	Erythro-blastosis
2	28	ii	Am.-Jewess		1—Icterus gravis	0	40	3	Spont.	Normal	
3	38	vii	Aust.-Jewess	3	1—Hy-drops fetalis	0	35	3	Spont.	Normal	
4	42	vi	Aust.-Jewess	0	0	+	37	33	Spont.	Normal	
5	26	ii	Am.-Jewess	0	0	+	36	3	Spont.	Normal	
6	22	iii	Am.-Jewess	0	1—Cong. anemia, recovered	0	40		Spont.	Normal	
7	24	ii	Am.-Italian	1	0	0	40		Cesarean section	Normal	
8	36	iii	Rum.-Jewess	0	0	+	40	14	Spont.	Normal	
9	29	ii	Am.-Jewess	0	0	0	40	12	Spont.	Normal	
10	38	iv	Am.-Jewess	0	0	0	38	8	Version, breech ex-traction	Normal	
11	33	iv	Am.	0	0	0	40	10	Spont.	Normal	
12	32	ii	Am.-Jewess	0	0	0	36	2	Spont.	Normal	
13	27	i	Russ.-Jewess	0	0	0	34	4	Spont.	Normal	
14	35	ii	Am.	1	0	0	38	8	Low forceps	Normal	
15	38	ii	Ger-man	0	0	0	40	14	Spont.	Normal	
16	28	ii	Am.-Jewess	0	0	0	40	22	Spont.	Normal	
17	23	ii	Amer-ican	0	0	0	40	9	Spont.	Normal	
18	38	v	Russ.-Jewess	3	1—Icterus gravis	0	39	15	Spont.	Normal	
19	26	i	Am.-Jewess	0	0	0	34	30	Spont.	Normal	
20	30	ii	Am.-Jewess	0	0	0	39	6	Spont.	Normal	

treated by this technique. The series reported by Hawksley and Lightwood, in 1934, however, shows unsatisfactory results with this method. Blood transfusion is the treatment of choice. Fifty to 75 c.c. of blood should be given at once and repeated as often as necessary to maintain constancy in the number of the red blood corpuscles and an ample level of hemoglobin. In Case 8 which recovered, polycythemia indicated the phlebotomy employed prior to the two transfusions administered. Blood by continuous intravenous infusion seems indicated when intensive jaundice is associated with a rapidly falling hemoglobin. In our series, 3 babies received no blood in any form or manner, and all died (Cases 11, 12, and 19). Two infants received a single injection of 20 to 30 c.c. of whole blood,

TABLE II. FINDINGS IN NEWBORN INFANTS WITH ICTERUS GRAVIS

CASE	SEX	BIRTH WT. (GM.)	ONSET OF JAUNDICE (HR.)	LIVER	SPLEEN	BLOOD STUDY				THERAPY			RESULT		COMMENTS
						HB. %	R.B.C. (M.)	NUC. CELLS	NUC. R.B.C. %	ONSET AFTER BIRTH (HR.)	SERUM	TRANS-FUSION	DIED (HR. AFTER BIRTH)	RECOVERED	
1	M	2,610	48			160	6.75	32,800	21	72		65 c.c.	120		
2	F	3,150	Birth	1 F*	0	107	4.50	33,200	16	Birth	50 c.c.	50 c.c.	15	+	Edema of scrotum and extremities, severe type
3	M	2,460	4	4 F	4 F	70	3.00	30,000	300	8					Autopsy refused
4	M	3,996	24	1 F	1 F		6.50	19,800	41	24		60 c.c. + 30 c.c. whole blood	36		
5	F	2,578	6	2 F	2 F	52	1.46	12,800	85	8		480 c.c.	28	+	Adequate therapy; cerebral hemorrhage
6	F		3	2 F	2 F	50	2.35	44,800	58	8		800 c.c.			Ict. index -400; sec. anemia after 4 mo.
7	M	3,290	Home de-livery	2 F	2 F	70	3.80	64,800	Innum.	26		70 c.c.	31	+	
8		2,940	Birth—yellow vernix	2 F		150	6.50	28,000	30	Birth		100 c.c.			Phlebotomy of 25-40 c.c. blood before each 50 c.c. transfusion
9	M	3,716	48		2 F	100	3.90	46,200	48	48		75 c.c.		+	
10	M	2,752	48	1 F	1 F	110	3.50		7	72		60 c.c.	76		Died shortly after transfusion—reaction?
11	M	3,632	Birth—yellow vernix	2 F	2 F	98	5.90	43,750	53	None			17		
12	M	2,550	48	1½ F	1½ F	94	4.50	5,650	0	None		20 c.c.	74		
13	F	2,298	Birth				3.00		Innum.	28		whole blood	31		
14	F	3,060	Birth	1 F	1 F	50	3.10	12,000	143	8		200 c.c.	66		Adequate therapy; cerebral hemorrhage
15	F	3,060	12	2½ F	1 F	100	1.43	29,450	90	30		280 c.c.		+	Therapy when child in extremis
16	F	2,780	24	1 F	1 F	80	2.90	32,500	22	24		60 c.c.	84		
17	M	3,088	9			70	4.70	14,500	59	14		60 c.c.	24		Autopsy refused
18	F	2,948	Birth							Birth		20 c.c. whole blood	11		Not recognized clinically.
19	F	2,550	36			50	1.78	117,600	Innum.	None	50 c.c.		72		No blood studies
20	F	3,088	48							48			60		Autopsy refused

*F, fingers below costal margin.

TABLE III. PATHOLOGIC FINDINGS IN ICTERUS GRAVIS

CASE	LENGTH (CM.)	WT. (GM.)	EDEMA	LIVER		SPLEEN		HEART	OTHER ORGANS WITH ERYTHROPOIESIS					CEREBRAL HEMORRHAGE	KERN-ICTERUS	PLACENTA		OTHER FINDINGS
				WT.—NORMAL 178 GM.	ERYTHROPOIESIS	WT.—NORMAL 12	ERYTHROPOIESIS	WT.—NORMAL 117 GM.	BONE MARROW	PANCREAS	KIDNEYS	ADRENALS	OTHERS			GROSS	MICRO.	
1	44	2,280	0	100	+	12	+	12	+	+	+	+	+	0	Normal	*		
3	44	2,340	Scrotum, lower extremities	162	+	40	+	21	+	+	+	+	Between galea and epicranium 0	0	Normal	*		
5	48	3,500	Scrotum, peritoneal cavity, 50 c.c.	170	+	32	+	30	+	+	+	+	Lateral ven- tricle and cisterna basalis 0	0	Normal	*		
7	53	3,450	Face, extremities	185	+	50	+	15	+	+	+	+	0	+	Wt. 700 gm.	Nuc. R.B.C. in vessels		

10	45	2,450	0	144	+	20	+	17	+	+	+	+	+	0	Normal	*	Patent foramen ovale and ductus arteriosus
11	47	3,700	0	102	+	10	+	32	+	+	+	+	0	0		Nuc. R.B.C. in vessels *	
12	46	2,900	0	110	+	15	+	15	+	+	+	+	0	0	Normal	*	Atresia of hepatic duct
13	45		Peritoneal cavity, 20 c.c.	80	+	20	+		+				0	0	Normal	*	
14			Pleural cav- ity, 20 c.c. Subcuta- neous	160	+	30	+	25		+	+	+	+	Upper sur- face of cerebellum	Normal	*	Atelectasis of lungs
16	48	2,790	0	105	+	14	+	12	+	+	+	+	0	0	Normal	*	Post mortem blood.
18			0	220	+	38	+	30	+	+	+	+	0	0	Normal	*	Innumerable normoblasts
19	47		Peritoneal cavity, 20 c.c.	128	+	12	+	17	+	+	+	+	0	0		*	Patent foramen ovale and ductus arteriosus

*Placenta not saved for microscopic examination.

†Normal weights of liver, spleen, heart for full-term newborn.

and 2 received 50 c.c. of serum intramuscularly. Only 1 survived (Case 2). Of the remaining 13 infants, 11 received transfusions alone. One received a transfusion of 65 c.c. followed by continuous transfusion. In 1, intramuscular injection of whole blood preceded transfusion. There were 9 deaths in this group of 13 infants, a mortality of 69 per cent. One infant (Case 10) died as a result of a reaction following transfusion, although the patent ductus arteriosus and foramen ovale found upon autopsy may have been auxiliary causes. In Case 5, advanced cerebral hemorrhage with compression of the midbrain precluded recovery. Case 14 showed cerebellar hemorrhage and pulmonary atelectasis. In these 3 infants, recovery could not be expected. In the remaining 6 cases, of which 4 were severe and 2 mild, adequate blood was administered by repeated transfusions. In the entire series of 20 infants only 5 survived, a mortality of 75 per cent. The five infants who recovered received prompt and repeated transfusions. The important maternal, fetal, and pathologic data of 20 cases of icterus gravis are summarized in Tables I, II, and III.

ANEMIA HEMOLYTICA NEONATORUM

Anemia hemolytica neonatorum represents that form of erythroblastosis in which pallor of the skin and mucous membranes is the most pronounced feature. It may be the healed phase of icterus gravis (Case 6, Icterus). As in hydrops and icterus gravis, the liver and spleen are enlarged and an increased number of normoblasts appears in the peripheral circulation. Edema is lacking.

The incidence of anemia neonatorum is difficult to ascertain. Mild cases may go unrecognized, or are considered as physiologic icterus, for mild jaundice often precedes anemia. In 15,334 deliveries, from Jan. 1, 1933, to July 1, 1939, only 3 cases were encountered, an incidence of 1 in 5,111 confinements. The mothers were all born in the United States. The parity was 2.6 and the average age 28 years. Case 3 was from a twin pregnancy. Its mate succumbed to icterus (Case 12, Icteric series). Case 2 in the anemia group was followed by a sibling with icterus gravis (Case 6).

The outstanding characteristic of congenital anemia is pallor of the skin and mucous membranes. Though this feature is apparent at birth it is generally obscured by jaundice. With recession of icterus, whiteness of the skin becomes pronounced. Pallor of the mucous membranes is noteworthy. In our series, pallor appeared within forty-eight hours in Case 1. In Case 3, however, it was not apparent until the seventh day, and in Case 2, was not manifest until the tenth day after birth. Antecedent icterus was present in each instance but was only of mild degree. The infants are listless, weak, and nurse poorly. Enlargement of the liver or spleen or both is noted, but generally to a lesser degree than observed in icterus gravis or hydrops. It was found in all our cases. There is no edema. Petechial hemorrhages of the skin are noted in the literature but were not present in our group.

As in other forms of erythroblastosis, persisting hematopoiesis in the liver and spleen is classical. The degree, however, is not as advanced as in hydrops or icterus. Extramedullary blood formation in other organs may be present. The bone marrow is hyperplastic. The placenta is grossly normal. The hematologic findings are essentially similar to those of icterus gravis. The number of nucleated red cells in the peripheral blood is reduced although still remaining above the normal. The hemoglobin ranged from 18 per cent to 53 per cent and the red cells from 850,000 to 2,600,000. Case 2 showed 45 per cent normoblasts on smear. In Case 3, normoblasts numbered 1 per cent on the third day. Myelocytes were found in Case 2.

The diagnosis of anemia neonatorum is easily established by the pallor, enlargement of the liver or spleen or both and the characteristic blood picture. The prognosis is good, but the disease may run a prolonged course. Diamond,

Blackfan and Baty indicate that the anemia may remain stationary or even become aggravated until the sixth week of life. At this time there is a return of a normal number of young erythrocytes. Finally, the hemoglobin and red cells increase to the normal though a 4-month interval may be required for complete restoration. Repeated small transfusions of 50 to 75 c.c. of citrated blood are the specific treatment. The amount employed, however, is varied in each instance depending upon the maintenance of an adequate number of red cells and a high hemoglobin level in the blood. Liver and iron in sufficient doses are important aids in the recovery.

CASE REPORTS OF ANEMIA HEMOLYTICA NEONATORUM

CASE 1.—Mrs. Y. C. (No. 173116), para iii, aged 31 years, American born, was admitted in labor Sept. 1, 1935. The first pregnancy in 1923 resulted in a spontaneous abortion at two and one-half months. The second pregnancy in 1924 and the third pregnancy in 1928 were uncomplicated. The last menses occurred on Nov. 20, 1933, and the estimated date of confinement was Aug. 27, 1934. Labor terminated by low forceps after twenty-three hours, resulted in the birth of an apparently normal female infant, weighing 3,360 Gm. Slight jaundice was first observed forty-eight hours after birth. There was definite pallor of the mucous membranes. The spleen reached 3 cm. below the costal margin. The liver was not felt. The blood study showed 1.8 million red cells and 32 per cent hemoglobin. Smears were not made. On the fourth day after birth, a direct transfusion of 75 c.c. of blood was administered. The child was definitely improved and nursed more vigorously. A second transfusion of 75 c.c. was administered on September 7 (the sixth day of life). On discharge from the hospital September 9, the hemoglobin was elevated to 70 per cent and the red cells numbered 2.9 million per cm. The placenta which weighed 440 Gm. showed no gross or microscopic abnormalities.

CASE 2.—Mrs. F. C. (No. AA34709), para i, aged 21 years, American born, was admitted April 2, 1935, immediately following her home delivery. The first pregnancy in 1934 terminated normally. The last menses occurred July 14, 1934, and the estimated date of confinement was April 30, 1935. Labor occurred on April 2, 1935 (thirty-sixth week) and terminated spontaneously in the birth of a female infant weighing 2,640 Gm. On the tenth day after birth, the infant presented marked pallor and slight icterus. It nursed poorly. The liver and spleen were found enlarged, and the latter reached the level of the umbilicus. A blood study revealed 1.35 million red cells and 50 per cent hemoglobin. Nucleated cells numbered 30,000. Upon differential smear 45 normoblasts were noted per 100 white cells. There were 41 per cent neutrophils, 31 per cent lymphocytes, 10 per cent myelocytes, and 11 per cent metamyelocytes. The child received a transfusion of 75 c.c. of citrated blood and several injections of liver extract. This was followed by marked improvement. Anemia, however, persisted and on April 15, thirteen days after delivery, the hemoglobin was only 35 per cent and the red cells 1.5 million. The use of liver extract was continued after the child was discharged from the hospital. Complete recovery ultimately followed.

CASE 3.—Baby A of twin pregnancy (see Case 12 of icteric group). Its mate, Baby B, died of icterus gravis seventy-four hours after confinement.

This infant became jaundiced the third day following delivery. Upon examination the liver and spleen were just palpable below the costal margin. The blood study revealed: Hb. 81 per cent, red blood cells 3.8 million, and 10,550 white cells. Only 1 per cent normoblasts were present on smear. The jaundice disappeared on the seventh day but pallor became pronounced. The child became listless and nursed poorly. The hemoglobin had dropped sharply and reached 53 per cent. The red blood cells numbered only 2,260,000. Sixty cubic centimeters of citrated blood were accordingly administered. As there was no improvement, a second transfusion of 80 c.c. was administered on the ninth day. Recovery thereafter was rapid. The baby was discharged on the twelfth day after birth in good condition.

SUMMARY AND CONCLUSIONS

1. Erythroblastosis fetalis is a disease of the blood-forming organs of the newborn and neonatal infant, which results in an anemia characterized by the presence of an excessive number of immature red blood cells in the circulation.

2. Hydrops fetalis, icterus gravis neonatorum, and anemia hemolytica neonatorum are the three clinical types of erythroblastosis. Overlapping features are not infrequent. Five infants in the icteric group presented circumscribed edema. Icterus was the first symptom in the three infants of the anemia group.

3. Erythroblastosis fetalis is not rare. Twenty-seven cases were encountered in 15,334 deliveries, an incidence of 1 in every 568 confinements. There were 4 cases of hydrops fetalis, 1 in 3,833; 20 cases of icterus gravis, 1 in 766, and 3 instances of anemia hemolytica, 1 in 5,111.

4. Persisting hematopoiesis in the liver and spleen is the dominant pathologic finding. The bone marrow is hyperplastic. Extramedullary hematopoiesis is often encountered in the pancreas, kidneys, and suprarenal glands.

5. The blood picture is distinctive. The hemoglobin and red cells are reduced but the color index is above standard. The total number of nucleated cells is increased with an abnormally high ratio of early red blood cells (normoblasts and erythroblasts).

6. A tendency for recurrence in successive pregnancies is noteworthy. Four such cases are reported in 19 mothers of the icteric group.

7. Recurrent stillbirths were observed in 75 per cent of mothers with hydropic children, and in 21 per cent of mothers who had delivered icteric progeny.

8. Multiparas are generally affected. The average parity for the entire series was 2.8.

9. Toxemia of pregnancy is above the normal incidence but of only moderate severity. It was noted in 50 per cent of the hydrops group and in 20 per cent of the mothers in the icteric group.

10. Premature labor is frequent. It was encountered in all of the hydrops cases and in 30 per cent of the icteric series. In hydrops fetalis the distended abdomen may cause dystocia. This was observed in 2 of 4 infants in the series.

11. Hydrops fetalis is the fatal type of erythroblastosis. All 4 infants in this group perished. Subcutaneous edema, ascites, enlargement of liver and spleen are the important clinical findings. The large edematous placenta is noteworthy.

12. Intrapartum diagnosis of hydrops fetalis is possible by x-ray examination. It should be routinely employed where a history of recurrent stillbirths or definite erythroblastosis is obtained.

13. Icterus gravis is a severe form of erythroblastosis. Fifteen of 20 infants succumbed. Jaundice is the most prominent symptom, but may not appear for twenty-four to forty-eight hours after birth. Enlargement of the liver and spleen is present. The blood picture is

typical. The basal ganglia may show biliary pigmentation ("kern-icterus"). Four such instances were found on post-mortem examination. Cerebral hemorrhage is frequent and often precludes recovery. The placenta is grossly normal.

14. Anemia hemolytica neonatorum is the mildest form of erythroblastosis. All 3 infants recovered. Pallor of the skin and mucous membranes may be anteceded by mild icterus. Enlargement of the liver and spleen, or both, and an increased number of normoblasts in the smear afford prompt diagnosis.

15. Early and repeated transfusions comprise the ideal method of therapy for icterus gravis. The 5 infants who recovered received such prompt treatment. Iron and liver extract are valuable adjuncts to transfusion in the anemia group.

16. A history of repeated stillbirths indicates careful search for erythroblastosis as the underlying cause. Where autopsy is not obtainable smears made from cord blood afford a prompt and efficient method of diagnosis.

We extend our thanks to Dr. M. Lederer for permission to review the autopsy material and to the members of the Departments of Obstetrics and Gynecology for the privilege of including their cases.

REFERENCES

- (1) *Diamond, L. K., Blackfan, K. D., and Baty, J. M.*: J. Pediat. 1: 269, 1932.
- (2) *Fanconi, C.*: Monatschr. f. Kinderh. 68 and 69: 129, 1937. (3) *Ferguson, J. A.*: Am. J. Path. 7: 277, 1931. (4) *Hampson, A. C.*: Lancet 1: 429, 1929.
- (5) *Hellman, L. M., and Irving, F. C.*: Surg. Gynec. Obst. 67: 296, 1938. (6) *Hellman, L. M., and Hertig, A. T.*: Am. J. Path. 14: 111, 1938. (7) *Hellman, L. M., and Hertig, A. T.*: AM. J. OBST. & GYNEC. 36: 137, 1938. (8) *Javert, C. T.*: Ibid. 34: 1042, 1937. (9) *Lightwood, R., and Hawksley, J. C.*: Proc. Royal Soc. Med. 27: 225, 1933 to 1934. (10) *Lippman, A. S.*: Am. J. Dis. Child. 27: 473, 1924.
- (11) *Macklin, M. T.*: AM. J. OBST. & GYNEC. 38: 14, 1939. (12) *Peck, H. A.*: New York J. Med. 35: 871, 1935. (13) *Witby and Briton*: Disorders of the Blood, Ed. 2, p. 327. (14) *White, R. R.*: J. M. Soc. New Jersey 31: 677, 1934.

Gaehdgens, G.: The Importance of Accessory Food Factors (Vitamins) in Gynecology and Obstetrics, Zentralbl. f. Gynäk. 62: 626, 1938.

The author presents a summary of all available information regarding the physiology and disturbances of vitamin metabolism in the gynecologic-obstetric field. The problems of avitaminosis are not of as great importance in this field as are the effects of hypovitaminosis. Not only does this condition depend upon intake but it is suggested that disturbances in the physiology of structures concerned in the final production of active vitamins (the liver and vitamin A, the skin and vitamin D) may play a part in the resultant hypovitaminosis. Known deficiencies in vitamin E in pregnancy and lactation are pointed out and the effects suggested. What little is known of the relationship of vitamin E to fertility is described.

An excellent case is made in stressing the lack of information available in this field and the probable value to be obtained from investigation. Very little is known of the results of hypovitaminosis as compared to avitaminosis, and it is in the former that the most pressing problems lie. No original or new work is presented.

J. L. McKELVEY.

RELATIONSHIP OF THE THYROID AND ADRENAL GLANDS TO THE TOXEMIAS OF PREGNANCY*

EDWARD C. HUGHES, M.D., SYRACUSE, N. Y.

*(From the Department of Obstetrics of the College of Medicine, Syracuse University,
and Syracuse Memorial Hospital)*

THE toxemias of pregnancy have presented a complex problem, in which there has existed an alteration in the chemistry and physiology of the body, producing the pathologic lesions which have been characteristic of the disease. Recent investigative work has brought forth the relationship of the electrolytes and hormones to these changes, and a decision as to their behavior may help to solve the mystery that surrounds the etiology of these conditions. The toxemias are problems far too intricate for the obstetrician alone to decide, and the expert opinion and judgment of the chemist, physiologist, histologist and pathologist are necessary to understand these unusual physical changes.

The purpose of this paper is not to promote any new theory concerning these things, but rather to review the work which has been done on them. The data which have been prepared have been obtained through the cooperation of the departments† of chemistry, physiology, histology, and pathology.

In order to more clearly understand the material presented, a short résumé of the recent research on the toxemias is presented, limiting the discussion to the glandular relationships.

Cushing was among the first to consider the possibility of glandular involvement in these conditions. He stated that a basophilic infiltration of the pars nervosa of the pituitary had occurred in eclampsia. Others found that associated with these infiltrations were similar changes in the cortex of the adrenal glands. Hofbauer stated that the toxemias were based upon a pituitary-adrenal relationship. George Van S. Smith, O. Watkins Smith, Rovak, Taylor and others have observed the importance of the anterior portion of the pituitary by the increase of prolactin that occurs in the late toxemias. However, there is some question as to the source of this prolactin. Taylor and associates have recently presented good evidence that there exists a relationship of estrogen and other placental hormones to the sodium and potassium balance during pregnancy. Thus, they have considered the ovary and placenta as factors in production of these conditions. Bartholomew and Colvin stated that adolescent gravidas with basal metabolic rates below plus 10 showed hypercholesterolemia, and were increasingly subjected to toxemias as the basal metabolic rate decreased. In 1934, I reported a series of 1,250 basal metabolic rates during pregnancy, in which a relationship between the level of metabolism and the early as well as late toxemias seemed to exist. In these studies the thyroid seemed to have some relationship to the toxemias.

*Read at a meeting of the Brooklyn Gynecological Society, March 1, 1940.

†For their valuable aid I am gratefully indebted.

It might be assumed from the foregoing that there must exist an imbalance of the glands of internal secretion during these conditions. However, we are impressed by the tremendous variation that may produce symptoms and signs, if we examine the values of these in any of these groups. In some, high concentration of hormones seems to produce symptoms, while in others nothing abnormal develops. It would appear that development of toxemia depends upon the ability of the individual to withstand the great glandular and metabolic changes that take place during pregnancy. We have been interested in the adrenals and thyroid during pregnancy and the toxemias, and feel that they play an important part in the production of some of the abnormal physiology that takes place during these conditions.

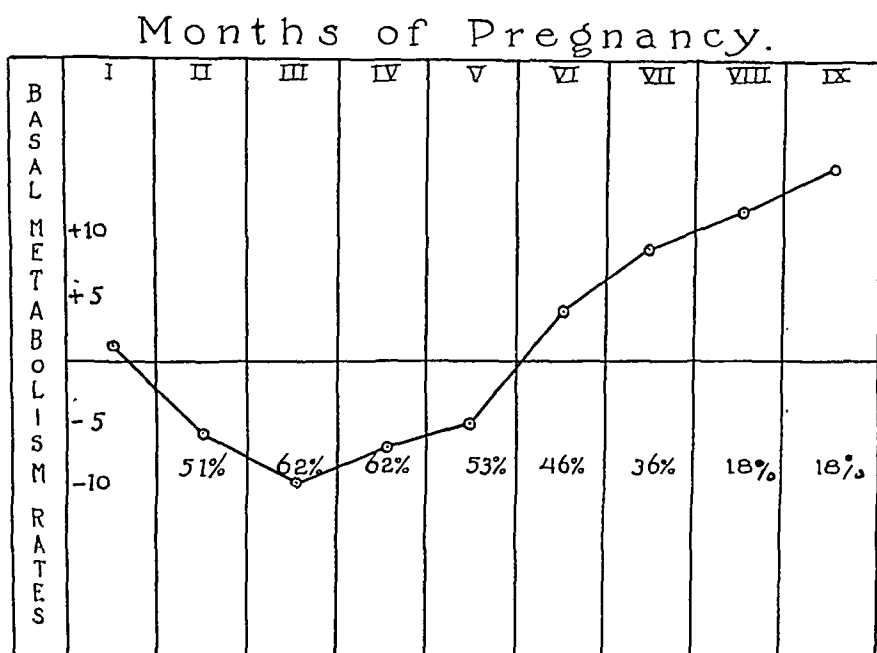


Fig. 1.

The following problems will be considered:

1. The relationship of the basal metabolic rate to the early and late toxic groups will be discussed.
2. The level of sodium in blood serum and urine in normal and abnormal pregnancy will be related.
3. The effect of injection of the urine of toxic patients upon the thyroid, adrenals, liver, and kidneys of rabbits will be described.

The relationship of the basal metabolic rate to normal pregnancy and the toxemias of pregnancy has been observed in a series of 400 private patients, therefore conditions could be made as basal as necessary. These findings differed slightly from those reported earlier, showing the advantage of a larger group of cases. These will be reported in detail elsewhere.

OBSERVATIONS

During the first trimester, there was a tendency for the basal metabolic rate to be below the zero line (Fig. 1). In the second and third months, the reading was below zero in 51 per cent and 62 per cent of the cases, respectively. During the second trimester, the readings showed an increase, and a greater percentage approached the zero line. In the fourth, fifth, and sixth months, the readings were below in 62 per cent, 53 per cent, and 46 per cent of the cases, respectively. During the third trimester, the rate had increased above the zero line, so that 63.3 per cent, 82 per cent, and 82 per cent were above zero in the seventh, eighth, and ninth months, respectively. In presenting this curve, it was realized that the values were within normal limits. However, the trend of the curve was the important observation, being below zero in the first trimester and above zero in the last trimester.

During the first trimester, many patients complained of the symptoms of subnormal metabolism, namely fatigue, exhaustion, and drowsiness. Certain other symptoms and signs also occurred during these months. Their relationship to the level of metabolism was noted in the four following groups of cases:

1. Those with basal metabolic rates above plus 10.
2. Those with rates between 0 and plus 10.
3. Those with rates between 0 and minus 10.
4. Those with rates below minus 10.

TABLE I

CASES	400	BELOW -10	0 -10	0 +10	ABOVE +10
		%	%	%	%
Moderate nausea		62	68.0	26.2	18.0
Moderate vomiting		61	40.0	10.3	10.0
Severe nausea		36	7.6	0	5.0
Severe vomiting		36	7.6	0	2.6
Fatigue		66	66.0	15.0	14.0

The percentages of the occurrence of early symptoms and signs are shown in Table I. Many patients showed a considerable drop in the metabolic rate as the symptoms and signs occurred. It was also apparent that thyroid given to these women did not improve the symptoms appreciably nor cause the usual elevation in the metabolism rate.

During the second trimester, the basal metabolic rate approached the normal. During these months, the hormonal content of the body was more balanced and few complications occurred.

During the third trimester, there occurred an elevation in the basal metabolic rate, the majority of the cases rising above zero. This was probably due to the excess hormonal production, increased weight, surface area, and protoplasmic mass. However, in several cases of twins and one case of triplets, the basal metabolic rate did not increase more than usual. The relationship of the development of pre-eclampsia and eclampsia was observed during this time. Eclampsia did not develop. Pre-eclampsia developed more often in the following types of patient:

1. When the basal metabolic rate was abnormally low during the first trimester, and failed to increase during pregnancy.
2. When the basal metabolic rate dropped appreciably to a low value and remained at this level throughout pregnancy.

In these groups, pre-eclampsia occurred five times more often than in the other groups. However, as the toxemias developed, the metabolism increased quite rapidly.

As a test of the value of basal metabolic rates during pregnancy, two series of patients were studied. The first series comprised 550 patients. In these cases, the prenatal care was thorough and adequate, but the metabolism was allowed to take its own course. Pre-eclampsia occurred in 5.2 per cent of the cases.

In the second series of 558 private patients, the same amount of prenatal care was given, but all patients with metabolism below zero were given thyroid extract in adequate doses to maintain a constant plus level. The incidence of pre-eclampsia in this group was 2.5 per cent. From these results it is felt that it is important to follow the basal metabolism from the onset of pregnancy.

The second portion of this paper deals with the effect of normal pregnancy and the toxic conditions of pregnancy upon the metabolism of sodium. Sodium is perhaps the most important base in the body, and is absolutely necessary for life. It is carried by the serum and the intercellular fluids almost entirely, and remains at a constant level. Among the conditions which alter the level of sodium in these fluids, perhaps insufficiency and overactivity of the adrenal cortex have the greatest influence. If the former condition prevails, sodium is lost

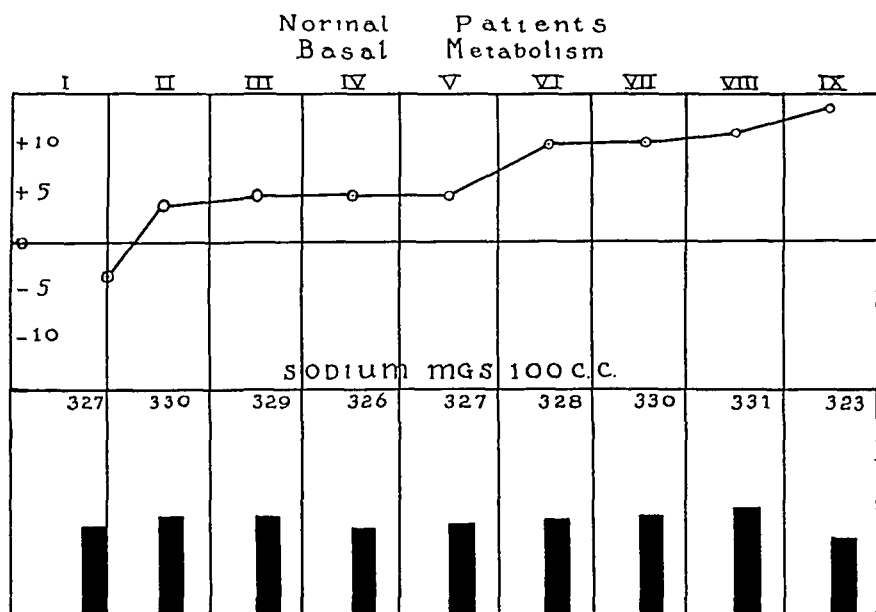


Fig. 2.

readily through the urine, thus causing a depletion of the sodium in the blood serum. If the latter condition develops, sodium is retained with water in the tissues. Other conditions causing loss of sodium are excessive vomiting, sweating, and diarrhea. During normal conditions, the intake and output of sodium maintain a constant balance, most of the sodium being excreted through the kidneys. Recent work has indicated that the metabolism of sodium is controlled by the adrenal cortex, and that reduction in the function of that gland is indicated by a high urinary output and a low serum value. Whether this criterion would be true during pregnancy when so many other factors are involved, is not known.

Sodium was determined in the serum and urine by using a modification of the Butler-Tuthill method. Values were expressed in milligrams per 100 c.c. of serum. Sodium determinations were made in three groups of patients:

1. Normal patients during pregnancy.
2. Patients suffering from mild and severe, early toxic conditions.
3. Patients having pre-eclampsia and eclampsia.

The first group consisted of 52 normal pregnant women. These individuals were placed upon diets containing 5 gm. of sodium and 10 glasses of water per day. It was impossible to place these women upon an absolutely controlled diet. However, careful instructions were given as to the diet, and it seemed accurate enough to be comparable. The values were surprisingly uniform. Basal metabolic tests were also done on the same day that the sodium was determined. In these patients no symptoms or signs occurred. Results are recorded in the following chart (Fig. 2).

The second group were patients suffering from nausea and vomiting of early pregnancy, and were classified as follows:

A. Twenty patients with nausea alone.

B. Twelve patients having emesis gravidarum.

Both groups were placed upon an intake of 5 gm. of sodium per day. The output of sodium was not recorded. These patients were not considered controlled studies, and were treated in the home or office.

C. Seven patients were classified as hyperemesis gravidarum.

These patients were all treated in the hospital and were seriously ill. Therapeutic abortion was necessary in two cases. Death occurred in one ward case. This group was carefully controlled for three days. Five grams of sodium were given in 2,100 c.c. of 5 per cent glucose intravenously per day. Nothing was given by mouth during the control period, so the amount of vomitus at each eructation was very small. Sodium estimations were made upon the vomitus and urine, but were not calculated upon the stool. It is interesting to note that the output of sodium in the urine was nearly equal to the intake (Tables II and III).

TABLE II. BASAL METABOLIC RATE AND SODIUM DETERMINED IN EARLY TOXEMIAS

	GROUP I (NAUSEA)	GROUP II (EMESIS GRAVIDARUM)	GROUP III (HYPEREMESIS GRAVIDARUM)
Total cases	20	12	7
Average blood pressure	115-80	94-80	90-60
Acetone in urine	0	36%	100%
Loss of weight	30%	93%	100%
Fatigue	50%	100%	100%
Sodium-Serum			
During symptoms	313.6 mg.	306.2 mg.	288.3 mg.
Lowest sodium	311.0 mg.	298.0 mg.	262.5 mg.
Highest sodium	323.0 mg.	314.0 mg.	305.0 mg.
After symptoms	325.3 mg.	326.8 mg.	325.4 mg.
Basal metabolic rate			
Drop from normal	60%	90%	*100%
Per cent below 0	85%	84%	-100
Average	-9	-11	- 18

*Only 3 patients had basal metabolic rate on account of condition.

TABLE III. CONTROLLED GROUP

HYPEREMESIS GRAVIDARUM		
Total cases	7	
Intake	2100 c.c. daily	
Output	1950 c.c. daily	
Sodium		
Average intake	5000.0 mg.	5.0 Gm.
Average output—urine	4029.5 mg.	4.02 Gm.
Average output—vomitus	700.0 mg.	0.700 Gm.
Average sodium-serum	288.0 mg.	0.28 Gm.
Average low	262.5 mg.	0.26 Gm.
Average high	305.0 mg.	0.30 Gm.

Two patients presented some notable findings. In one, the blood plasma sodium reached a level of 262 mg. per 100 c.c. of serum. At this point, the patient was in severe shock, blood pressure and pulse imperceptible, and condition was very grave. The excretion of sodium in the individual was very low, the average being 26.6 mg. per day. However, the output of urine was very scanty, total 450 c.c. per day. This showed that when the sodium and chloride reached a dangerously low level, the kidneys either attempted to restrict their output, or were so severely damaged that they failed to excrete.

The second patient, after the control period, was given 10 Gm. of sodium with 5,000 c.c. of fluid per day. The output of urine about equalled the intake, and the sodium excretion rose to 12.5 Gm. This shows that the output of sodium is also dependent upon the output of water. With a low threshold of sodium in the kidneys that may exist at this time, the water washes the sodium out of the system sooner than it would during the normal states.

It was also noted that of the 5 patients cured of hyperemesis, 2 became toxic in the latter months of pregnancy and labor had to be induced. In these women, the level of sodium was slow to rise to normal, and not until the normal was reached were these women free from symptoms.

Sodium determinations were made in three groups of patients presenting the typical picture of the true late toxemias of pregnancy. The type of onset and follow-up examinations substantiated these facts. There occurred the usual

TABLE IV. LATE TOXEMIA GROUP—UNCONTROLLED

	PRE-ECLAMPSIA	ECLAMPSIA
Total cases	12	6
Av. Blood pressure	182-115	186-126
Edema	100 %	100 %
Albumin	1+—0.30%	0.10%—0.44%
NPN	27	24
Total proteins	5.7	5.6
Fluid		
Av. intake	1776 c.c.	2100 c.c.
Av. output	810 c.c.	700 c.c.
Sodium	Serum—mg. per 100 c.c.	
During condition	304.4	298
After delivery—10 days	327.2	329

TABLE V. CONTROLLED GROUP

	PRE-ECLAMPSIA	
Total cases	14	
Fluids—average		
Intake	2100 c.c. daily	
Output	1188 c.c. daily	
Sodium	Serum—mg. per 100 c.c.	
Av. during control	307.3 mg.	
Lowest Na	295.0 mg.	
Highest Na	317.0 mg.	
Sodium		
Average intake	5000.0 mg.	5.0 Gm.
Average output, per 24 hr.	1728.4 mg.	1.7 Gm.
Av. output, per 100 c.c. urine	162.5 mg.	0.162 Gm.
Lowest output, per 24 hr.	575.0 mg.	0.57 Gm.
Highest output, per 24 hr.	2873.0 mg.	2.8 Gm.
Lowest output, per 100 c.c.	57.0 mg.	0.057 Gm.
Highest output, per 100 c.c.	268.0 mg.	0.268 Gm.

disturbance in water balance, as shown by the presence of edema, low plasma proteins, scanty urine, and albuminuria. The usual symptoms and signs, such as headache, disturbance of vision, and high blood pressure, were also present. Although the patients in Groups I and II were placed upon 5 Gm. of sodium intake, they were not controlled studies.

The third group consisted of 13 cases of pre-eclampsia. In this group, a simple diet of milk, orange juice, toast, crackers, and sodium to make a total of 5 Gm. per day, was given. The total fluid intake was 2,100 c.c. per day. There was no vomiting. Sodium excretion by bowel was not determined. The urinary output was carefully estimated. The data are as shown in Tables IV and V.

DISCUSSION

In consideration of these findings, it would seem that the level of sodium was disturbed but little during normal pregnancy. In abnormal conditions, such as nausea and vomiting that occur in the first trimester of pregnancy, the threshold for sodium in the kidneys may be at a lower level than normal, and allow this base to be excreted more readily. Also, sodium was probably lost in the vomitus to a greater extent than even shown in these studies, because in these particular patients the amount of vomitus was small as compared with the average case. The loss of sodium in these two ways reduced the amount in the serum to unusual and dangerous levels.

The balance of sodium was again disturbed when pregnancy was complicated in the last trimester by preeclampsia and eclampsia. In these cases, where the intake of sodium was the same as in the other group (namely 5 Gm.), the amount of sodium in the blood serum was again low (average 297 to 304.4 mg.). The excretion of sodium by the kidneys was considerably less than normal or in the early complications. The first question that arose was how to explain the low serum value when the output of sodium through the kidneys was so small. Our tentative interpretation was as follows: The serum proteins were below normal, probably being lost in the urine. This caused the osmotic pressure in the capillaries to be diminished. This fact, coupled with the rise in blood pressure and increased permeability of the capillary wall, drove the fluid into the tissue spaces. The sodium was moved with the water and passed into the tissues. There occurred an actual retention of sodium and chloride, even though the concentration in the serum was below normal. In other words, the amount of sodium is the same per 100 c.c. of serum as it would be per 100 c.c. of tissue fluid. As soon as the kidneys started to put out water after delivery, then sodium was abstracted from the tissues into the circulation and was excreted. Just that situation occurred after delivery of these patients. The urinary output increased markedly, and again the sodium in the serum was at a low level, owing to the rapid excretion in the urine.

The next question that presented itself, was what influence upon the kidneys was present during these times which would cause sodium to be excreted more readily during the early toxic conditions and retained during the late conditions. Also, what had caused the proteins to be lost in the urine so readily in pre-eclampsia and eclampsia. Taylor and associates had considered that the estrogenic and placental hormones had influenced the sodium and potassium excretion. Engel

and Thorn had thought that the edema during the menstrual period was caused by progesterone. Inasmuch as the adrenal cortex controls the sodium and perhaps the water metabolism, this structure could also play an important part in the production of edema. If any of these products of glandular activity had produced these changes, their presence should be found in the urine in abundance. With this thought in mind, urine from those patients described earlier was injected into rabbits in an attempt to reproduce the pathologic findings of these toxic conditions. All rabbits were mature virgins, weighing approximately 3000 Gm.

Sixty cubic centimeters of urine were given intravenously in each case, and the animal killed by a blow on the neck fifty-two hours later. They were autopsied immediately. Although all of the endocrine glands are being studied, only the effect on the thyroid and adrenals will be reported at this time. The effect on the liver and kidneys will also be reported.

Five groups of rabbits were studied:

1. Six rabbits were injected with 60 c.c. of urine from normal patients eight to ten weeks pregnant.
2. Four rabbits were injected with 60 c.c. of urine from patients described earlier in this paper as hyperemesis gravidarum.
3. Ten rabbits were injected with 60 c.c. of urine from patients classified as pre-eclampsia and eclampsia.
4. Seven rabbits were injected with 60 c.c. of urine from normal pregnant women at term.
5. Ten pregnant rabbits were killed at various stages of their pregnancy. They had not been injected.

On account of the lack of space, it is impossible to show the structures of Groups 4 and 5. Examination of these structures showed normal thyroid and adrenals with the exception of some hyperplasia as term approached. Also, there were no liver or kidney changes. There was some slight change in the thyroid, adrenals, liver, and kidneys of those rabbits injected with term urine. However, these changes were not considered significant.

The changes in the structures of Groups 1, 2, and 3 will be shown in Figs. 3 to 11.

Injection of urine from normal, early pregnant patients, and those suffering from hyperemesis gravidarum has produced changes in the structures of the thyroid and adrenal glands of the rabbits. Examination showed the follicles of the thyroid were uniformly large with a store of colloid. The cells lining these follicles seem uniformly flat with small nuclei. These findings would indicate a gland of low activity. The adrenals of these same rabbits also showed signs of altered function. The cells of the reticular layer of the cortex showed some unusual characterization. Some cells were gathered in clusters, and the cytoplasm was very pale, vacuolated and without granulation. The nuclei were also shriveled, pushed to one side and were smaller than normal. Some whole cords of cells were affected in a similar manner, the extension reaching to the glomerular zone. These cells did not take a fat stain. Inasmuch as these rabbits were all mature and of good size, any change that would take place in early life could be ruled out. There occurred necrosis with hemorrhage about the central vein in the liver of three of the four rabbits in Group 2. Also, there

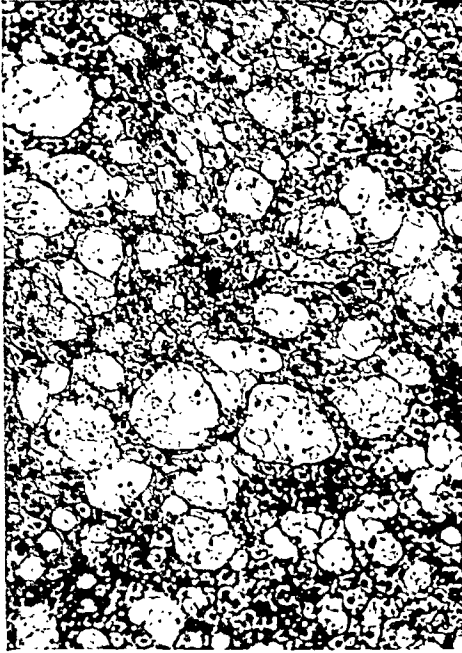


Fig. 3.



Fig. 4.

Fig. 3.—Adrenal cortex. Low power $\times 150$. Rabbit I, injected with 60 c.c. of urine from a patient ten weeks pregnant. Patient had nausea and vomiting of moderate degree. Vacuolated cells shown in Figs. 1 and 2 were found in the reticular zone of the adrenal cortex.

Fig. 4.—Adrenal cortex. High power $\times 600$. Rabbit I. Cluster of cells showing vacuolation. Nuclei of these cells are shrunken and pushed to one side. Cells distended, possibly early degenerative changes.

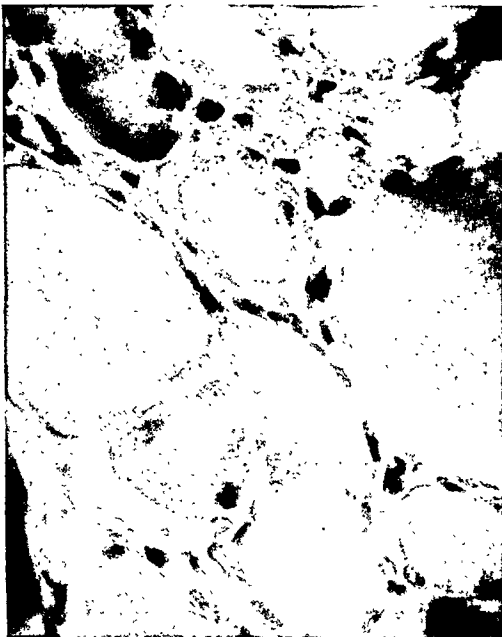


Fig. 5.

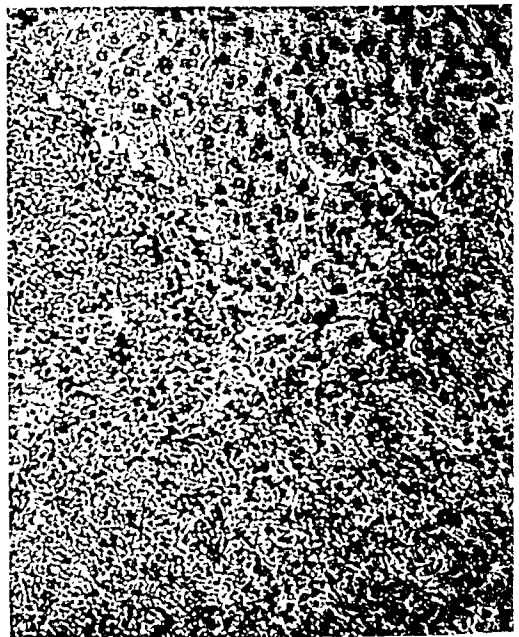


Fig. 6.

Fig. 5.—Thyroid. High power $\times 600$. Rabbit I. Follicles are uniformly large, filled with colloid. Cells lining the follicles are flat with elongated nuclei. Low activity gland.

Fig. 6.—Liver. Low power $\times 150$. Rabbit H. Necrosis with hemorrhage occurred about central vein. Fatty degeneration occurred about central vein, also.

occurred a bleaching out of the cells about the central vein in three rabbits, and distinct necrosis with hemorrhage in two others of Group 1.

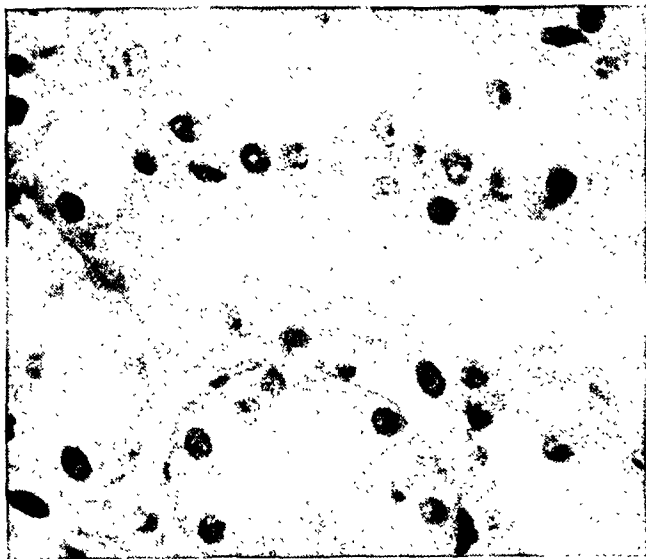


Fig. 7.—Kidney. High power $\times 600$. Rabbit I. Sloughing of cells of the proximal secreting tubules.

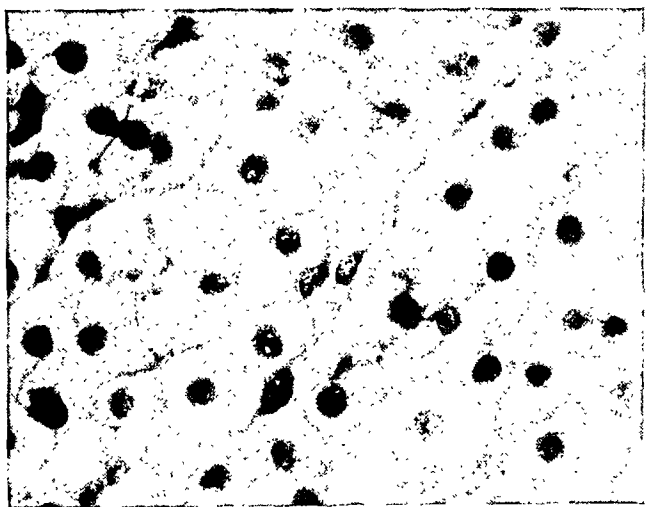


Fig. 8.—Adrenal cortex. High power $\times 600$. Rabbit M. This rabbit was injected with 60 c.c. of urine from an eclamptic patient seven months pregnant. Cells are smaller, no vacuolization, cords of cells were longer, and cells appear more active.

The damage in the kidneys was not as extensive, but there was some sloughing of the cells in portions of the distal and proximal secreting tubules. These changes were even more marked when injected into pregnant rabbits.

The structures from rabbits in Group 3 have shown a different picture. The thyroid seemed to be one of activity. The average follicle was smaller with less colloid. In some follicles the colloid had nearly disap-

peared. They were lined by more cuboidal types of cells. The nucleus was larger and more active. The adrenal cortex also appeared different. The cells were smaller, the cords were longer and appeared more active. The large, vacuolated cells observed in Groups 1 and 2 did not occur in a single case. There were more mitotic figures in the glomerular area.

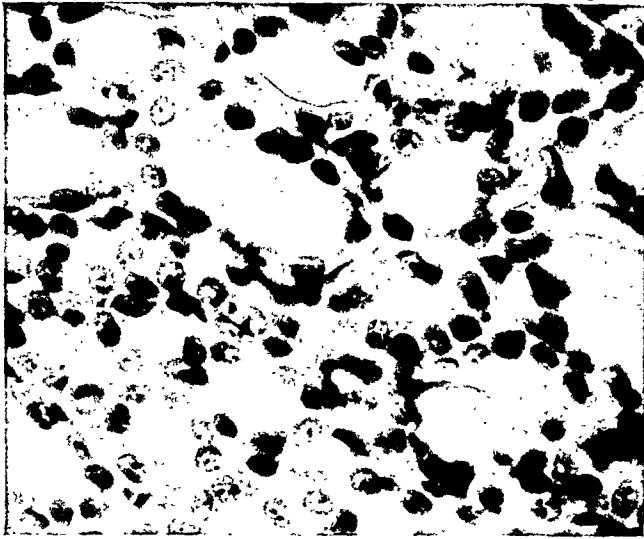


Fig. 9.—Thyroid. High power $\times 600$. Rabbit M. Follicles are uniformly smaller and contain less colloid. The cells lining the follicles are more colloidal with more oval nuclei. The gland appears to be more active.

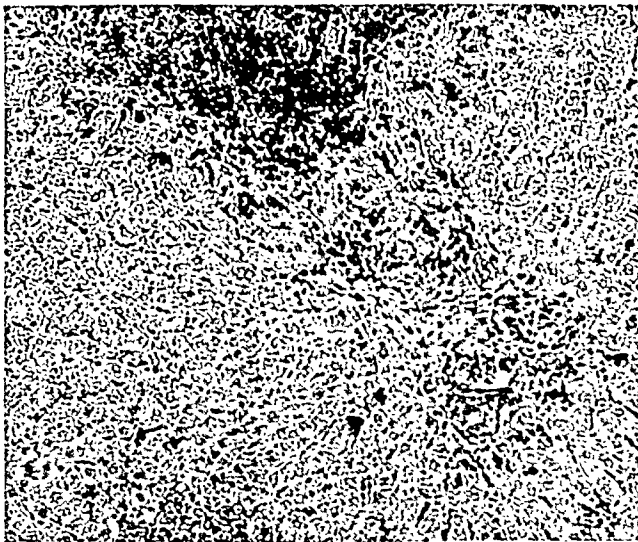


Fig. 10.—Liver. Low power $\times 150$. Rabbit M. Area of necrosis with hemorrhage occurred about the outside of the lobule or periportal. Fatty degeneration also occurred about the same area.

The liver from these rabbits also presented a different picture. In 5 rabbits, the cells about the periphery of the lobule were involved. Necrosis and hemorrhage appeared here. The kidney likewise showed the sloughing of cells in the distal portion of the secreting tubules.

It would appear that some product of metabolism or some other material, perhaps hormonal in nature, had been produced in these patients where a general metabolic change had occurred, and also where the sodium content was altered. This material had been excreted in the urine, which when injected into rabbits, produced the changes in the structures described previously. These lesions were typical of those found in early and late toxemias.

When considering what the nature of this material might be, many possibilities arise. The question of the influence of the hormones of the anterior lobe of the pituitary and those hormones simulating those from this gland is important. It would seem that if these conditions were due to these structures the findings would be the same when urine from early and from late toxic cases were used. However, this

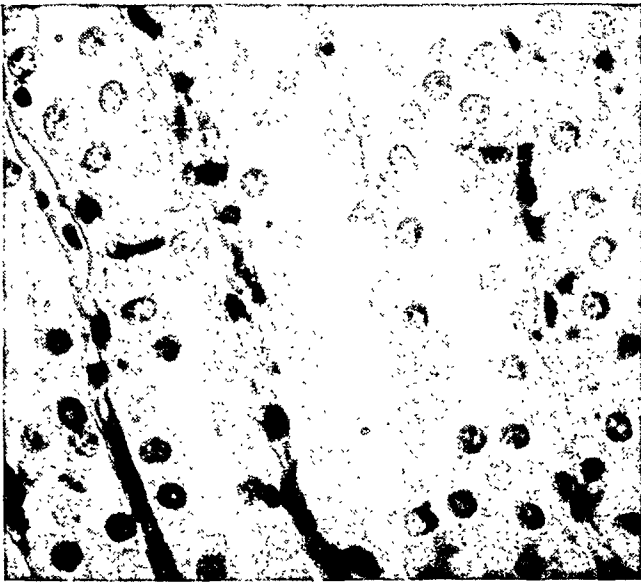


Fig. 11.—Kidney. High power $\times 600$. Rabbit M. Sloughing of the cells lining the distal secreting tubules is shown.

did not occur, the thyroid and adrenals differed in each group, and the lesions in the liver occurred at opposite sides of the lobules. Therefore, it would seem either that the high prolan values found to occur in the later toxic conditions were from a different source or of a different type, possibly placental in origin. Also the question arises if the cortex of the adrenal glands might not be the offending structure, being depressed in function early in pregnancy and overactive in late pregnancy. Also, the placenta and fetus cannot be forgotten as producing hormones yet undiscovered, which may explain all of these conditions. Then the possibility of the corpus luteum becoming too active brings up another source of material. If we disregard the hormone situation, the discussion takes us to some metabolite, perhaps an amino acid. In any event, further work must be done, and perhaps by the combined efforts of all, some advances will be made to solve the mystery which surrounds these conditions.

CONCLUSIONS

1. Basal metabolic rates indicated that pregnancy has an affect on the glands controlling metabolism. This was indicated in the first and third trimesters.
2. Administration of thyroid to those with low rates in the first trimester reduces the incidence of the late toxemias 50 per cent, but must be given early in pregnancy.
3. Serum sodium is lowered during the early and late toxemias, but remains constant throughout normal pregnancy.
4. Sodium is excreted in the urine in greater quantities in the early than in the late toxemias.
5. Sodium in the serum is lowered in pre-eclampsia and eclampsia because of loss of serum protein and water accumulation in the tissue spaces.
6. Injection of early and late toxic urine into virgin rabbits produces lesions in the thyroid and adrenals. The pathologic changes in the liver and kidneys were typical of early and late toxemias of pregnancy.
7. The late group of toxemias presented a different hormonal picture from the early.
8. The question arises as to whether these changes mean hormonal imbalance, or overproduction of some toxic metabolite, or both.

I wish to express my sincere gratitude to the Departments of Chemistry, Microscopic Anatomy, Pathology and Physiology for their cooperation in this work.

I also wish to express my appreciation to Miss Anne Coplon, technician, for her efforts.

REFERENCES

- Anselmino, K. J., and Hoffman, F.: *Ztschr. f. Geburtsh. u. Gynäk.* 114: 52, 1936. Bartholomew, R. A., and Colvin, E. D.: *AM. J. OBST. & GYNEC.* 36: 909, 1938. Butler, A. M., and Tuthill, Elizabeth: *J. Biol. Chem.* 93: 171, 1931. Cushing, Harvey: *Proc. Soc. Exper. Biol. & Med.* 30: 1424, 1933. *Idem*: *Am. J. Path.* 10: 145, 1934. Denis, W., and King, E. L.: *AM. J. OBST. & GYNEC.* 7: 253, 1924. De Snoo, K.: *AM. J. OBST. & GYNEC.* 34: 911, 1937. Gamble, J. L., Ross, G. S., and Tisdall, F. F.: *J. Biol. Chem.* 57: 633, 1923. Harrop, G. A., and Thorn, G. W.: *Assn. Am. Physicians Trans.* 52: 164, 1937. Hofbauer, J.: *Zentralbl. f. Gynäk.* 42: 575, 1918. *Idem*: *Klin. Wchnschr.* 12: 369, 1933. Holmes, Benjamin, and Kirk, P. L.: *J. Biol. Chem.* 116: 377, 1936. Hughes, E. C.: *N. Y. State J. Med.* 34: 873, 1934. Hummel, F. C., Sternberger, H. R., Hunscher, H. A., and Macy, I. G.: *J. Nutrition* 11: 235, 1936. Krebs, O. S., and Briggs, A. P.: *AM. J. OBST. & GYNEC.* 5: 67, 1923. Macciota, M.: *Riv. ital. di ginec.* 21: 58, 1938. McGuigan, H. A., and Higgins, J. A.: *Am. J. Physiol.* 114: 207, 1935. Rakoff, A. E.: *AM. J. OBST. & GYNEC.* 38: 371, 1939. Rossenbeck, H.: *Arch. f. Gynäk.* 145: 331, 1931. *Idem*: *Schweiz. med. Wchnschr.* 57: 1067, 1927. Schwarz, O. H., and Dieckmann, W. J.: *AM. J. OBST. & GYNEC.* 18: 515, 1929. Smith, G. Van S., and Smith, O. W.: *Ibid.* 38: 618, 1939. Stander, H. J., Duncan, E. E., and Sisson, W. E.: *Johns Hopkins Hosp. Bull.* 36: 411, 1925. Strauss, M. B.: *Am. J. M. Sc.* 194: 772, 1937. *Idem*: *Ibid.* 195: 723, 1938. *Idem*: *AM. J. OBST. & GYNEC.* 38: 199, 1939. Taylor, H. C., Jr., Warner, R. C., and Welsh, C. A.: *Ibid.* 38: 748, 1939. Thorn, G. W., and Engel, L. L.: *J. Exper. Med.* 68: 299, 1938. Thorn, G. W., Engel, L. L., and Eisenberg, Harry: *J. Exper. Med.* 68: 161, 1938. Thorn, G. W., and Harrop, G. A.: *Science* 86: 40, 1937. Thorn, G. W., Nelson, K. R., and Thorn, D. W.: *Endocrinology* 22: 155, 1938.

THE TREATMENT OF OLIGURIA AND ANURIA*

WILLIAM J. DIECKMANN, M.D., AND S. KRAMER, PH.D., CHICAGO, ILL.
(From the Department of Obstetrics and Gynecology, The University of Chicago, and
The Chicago Lying-in Hospital)

THE definitions of oliguria (a diminished output of urine) and anuria (a suppression of urine) are inadequate in that no period of time is designated to constitute a diagnosis of either condition, and the amount of urinary output, as a criterion for the use of the term, is not specified. It is our opinion that oliguria should be defined as the excretion of less than 600 c.c. of urine within twenty-four hours, and anuria as the absence of urine for twelve or more hours. Thus the occurrence of oliguria would be quite frequent in obstetrics, but anuria would be rare.

Oliguria or anuria is found with varying degrees of frequency in the following conditions:

Toxemia of pregnancy (eclampsia, pre-eclampsia).

Dehydration:

- (a) Due to loss of water (hyperemesis gravidarum, prolonged abdominal operations, peritonitis, intestinal obstruction, and diabetic coma).
- (b) Due to loss of blood (abruptio placentae, post-partum hemorrhage, placenta previa, rupture of the uterus, and ectopic pregnancy).

Blood transfusion reactions (incompatible and compatible blood).

Shock.

Ligation of both ureters.

Cortical necrosis of the kidneys.

We have previously described the treatment of a number of these conditions, and, therefore, we shall limit our remarks to the treatment of oliguria associated with blood transfusion reactions.

It is most difficult to treat oliguria and uremia following an incompatible blood transfusion. The mortality rate due to blood transfusion, according to various reports, ranges from 0.013 to 1.3 per cent; almost all the deaths are preventable. We have given over 1,200 blood transfusions since 1931, with evidences of serious reactions in 8 cases. We know that 4 patients were given incompatible blood, 3 received less than 100 c.c., and 1 received over 500 c.c., but none died. All patients had hemoglobinuria, but only the latter patient had uremia. Four other patients were given what was thought to be compatible blood and all died. Chemical analyses done on two patients revealed that the blood nonprotein nitrogen was 241 and 213 mg. per cent, respectively. Oliguria was present in all patients and serious infection was also an important factor in 3, but if the renal function had been normal it is presumed that all of them would have recovered.

*Presented before the Chicago Gynecological Society, February 16, 1940.

Over 300 blood transfusions were given on the obstetric service of Washington University, with one case of uremia, with recovery. The patient was given compatible blood, but developed oliguria, with a blood nonprotein nitrogen of 138 mg. per cent. Eight hundred cubic centimeters of a 30 per cent glucose solution were injected intravenously, twice daily, for seven days. Another patient, with an extensive carcinoma of the cervix, developed a puerperal infection following delivery, and was finally treated with radium. Donors, whose blood early in the puerperium caused no reaction, invariably caused hemoglobinuria after the radium treatment. This occurrence has not been noted in other patients after radium treatment, and we believe that the infection was a factor in producing heterologous hemagglutinins. We also had an opportunity to study a patient on another service who was given 500 c.c. of incompatible blood. The hemolysis of the erythrocytes produced a severe acidosis. The patient lived one and one-half hours. The CO_2 was 9 volumes per cent and the pH was 6.9.

Comparatively little importance is given in most hospitals to eliminating the dangers of blood transfusion. The typing, matching, and transfusion are usually performed by technicians and interns who have been given no instructions or have only a rudimentary knowledge.

DeGowin and co-workers have studied the cause and prevention of blood transfusion reactions, and they advise that one individual with experience should be in charge. All typing sera should be of high titer. They have five donors who were thought to belong to Group O and who gave transfusions, but were subsequently found to belong to Group A. One patient died from a transfusion given by one of these donors. It is important to check the donor's cells against the recipient's serum for both *agglutination* and *hemolysis*.

In attempting to determine the cause of the oliguria in one of our patients, we found that the cells were agglutinated, but hemolysis occurred so rapidly that the clumping was present for only a few seconds. One of the authors (W. J. D.) emphasizes the importance of matching the blood in small test tubes so that hemolysis can be seen. DeGowin states that hemolysis may occur without hemoglobinuria. Drabkin, Widerman, and Landow found that only 10 per cent of the hemoglobin disappearing from the plasma appears in the urine. DeGowin states that one should look for evidence of hemolysis in the blood serum within two hours after the transfusion.

Oliguria has been attributed to the following:

1. *Blocking of the Tubules by Precipitated Hemoglobin.*—Baker and Dodds have proved that this phenomenon occurs in rabbits, and DeGowin and co-workers found the same in dogs. Alkalinization of the urine will prevent oliguria in both dogs and rabbits after an intravenous injection of hemoglobin. The precipitated hemoglobin has been found also in the human kidney, but DeGowin has reported several cases of fatal oliguria and uremia after blood transfusion in which no hemoglobin was found in the tubules.

2. Renal lesions are due to a loss of chloride. Chemical analysis disproves this.

3. Anaphylaxis.

4. Nephrotoxic substances are set free by the hemolysis of the erythrocytes.

5. The liberated hemoglobin exerts a vasoconstrictor action on the renal vessels and the ischemia is the cause of the oliguria and renal pathology.

DeGowin concludes that there is still an additional unknown factor which causes the uremia. He advises that, whenever possible, the recipient's urine should be alkalized prior to the transfusion.

A compilation of the cases of serious blood transfusion reactions reported by Goldring and Graef, Bordley, DeGowin, together with ours, reveals that there were 11 males, with 6 deaths, and 29 females, with 15 deaths. Thirteen of the females were obstetric patients, with 6 deaths, and 7 were gynecologic patients, with one death. We have referred in

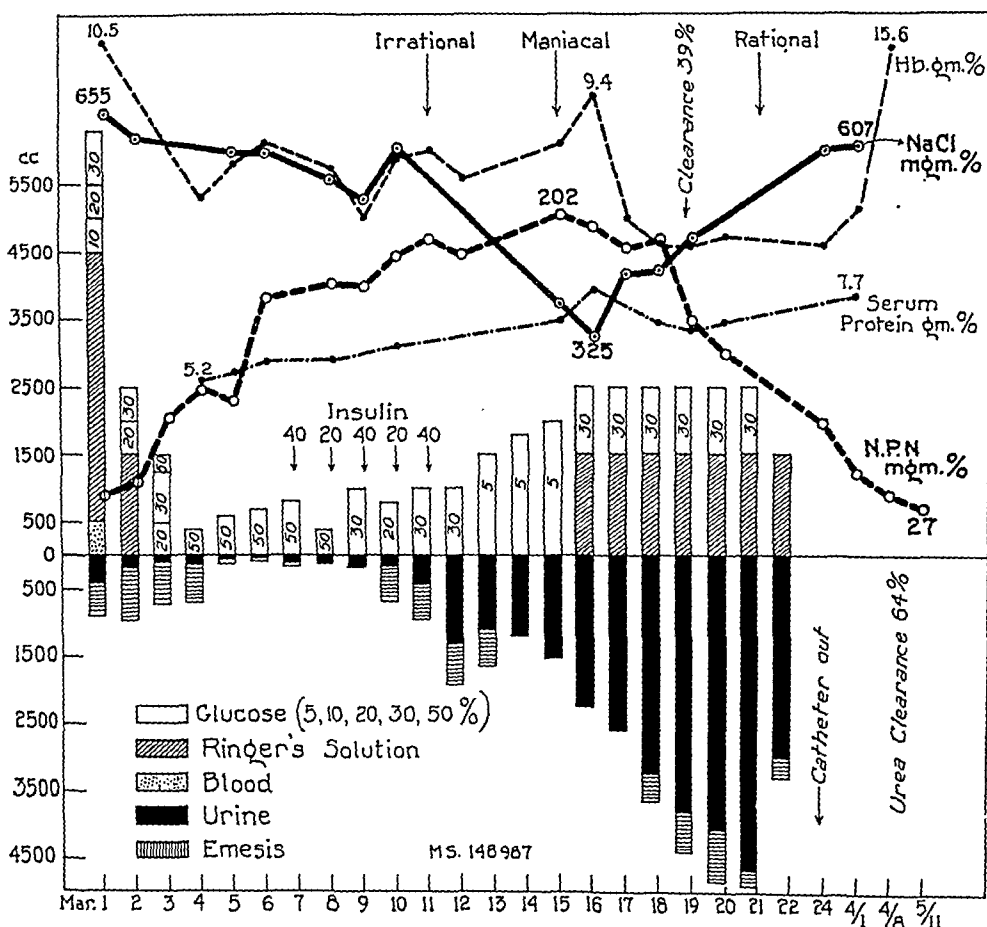


Fig. 1.—Chart showing oliguria and uremia due to an incompatible blood transfusion given in 1937. Examination of the patient on Feb. 6, 1940, revealed: Blood pressure, 100/80; urea clearance, 70 per cent; U/B, 7; serum protein, 6.9 Gm. per cent; and hemoglobin, 13.1 Gm. per cent. Urinalysis: Albumin negative; volume large; microscopic examination, essentially negative.

a previous article to the difficulty encountered in obtaining compatible donors for anemic patients with puerperal infection because of the marked rouleaux-formation of all erythrocytes suspended in the patient's serum. Therefore, for many years we have preferred to use Moss Group IV donors because their cells contain no agglutinogens. We also propose to adopt DeGowin's suggestion to alkalize the urine of all patients who are given a transfusion.

The volume and the color of the urine should be examined carefully for forty-eight hours after every transfusion. If an oliguria or hemo-

globinuria is found, a hypertonic glucose solution should be injected intravenously in large amounts, and sufficient alkali also should be given intravenously to maintain an alkaline urine until the latter no longer contains hemoglobin.

The following solution will alkalize the urine if the plasma CO_2 is within normal limits:

5 c.c. molar sodium lactate	} Per kilogram of body weight
25 c.c. distilled water	
20 c.c. Ringer's solution	

One-half of the solution should be given intravenously and the remainder by hypodermoclysis. One cubic centimeter of molar sodium lactate per kilogram of body weight given by mouth will maintain an alkaline urine, once the latter has been established. Twenty grams of sodium bicarbonate in a 5 per cent solution, given intravenously, may be used instead of the lactate, and this will raise the plasma CO_2 content approximately 15 volumes per cent in a woman weighing 60 kilograms, and also alkalize the urine. The secretion of urine is stimulated by intravenous injections of 1,000 c.c. of a 20 per cent glucose solution given at intervals, in order to maintain a urinary output of at least 60 c.c. per hour. The amount of fluid given within twenty-four hours should not exceed the urinary output by more than 50 per cent. If the urinary output amounts to less than 600 c.c. within twenty-four hours, a 50 per cent solution of glucose should be given in 200 c.c. amounts every six to eight hours. No water should be given orally or rectally, as it not only does no good but may increase the vomiting, thus eliminating the chloride from the stomach, or it will cause edema if it is retained. Electrolyte solutions are of use initially and they should be used only after the first forty-eight hours, if an analysis of the blood reveals that they are requisite.

Data, in Table I and Fig. 1, illustrate the treatment of a patient who was given incompatible blood. This patient had a dilatation and curettage, with a blood transfusion, for an incomplete abortion. A marked hemoglobinuria developed and persisted for several days. It is evident that an anuria almost occurred. Two hundred

TABLE I. TREATMENT OF PATIENT GIVEN INCOMPATIBLE BLOOD

DATE	URINE			BLOOD	
	24-HR. VOL. (C.C.)	NaCl (GM. PER DAY)	N.P.N.	URIC ACID (MG. PER CENT)	CREATININE (MG. PER CENT)
3/ 1/37	400			4.5	4.6
3/ 2/37	180				
3/ 3/37	90	0.55	0.21		
3/ 4/37	140	0.18	0.09	10.9	11.1
3/ 5/37	60	0.13	0.06	10.9	15.0
3/ 6/37	30	0.15	0.06	13.8	17.5
3/ 7/37	105	0.52	0.17		
3/ 8/37	110	0.39	0.08	18.3	20.7
3/ 9/37	150	0.79	0.49	21.1	21.4
3/10/37	285	1.4	0.47	19.0	22.6
3/11/37	435	2.39	2.85	19.0	24.0
3/12/37	1300			18.9	22.1
3/13/37	1110	3.17	4.4		
3/14/37	1170	2.2	8.9		
3/15/37	1525	0.78	5.5	16.4	18.8
3/16/37	2250	2.38	13.3		
3/17/37	2600	2.38	15.2	11.2	16.7
3/18/37	3250	2.98	14.6	9.7	15.4
3/19/37	3800	3.42	12.6	9.2	12.1
3/20/37	4050	2.85	6.3	5.6	10.6
3/21/37	4700	7.17	11.7		
3/22/37	3000	10.0	8.9		
3/23/37	3260	8.54	6.9		
3/24/37	3450	7.28	6.1		
3/25/37	4660	11.9	9.97		

cubic centimeters of a 50 per cent glucose solution were given three or four times daily. Insulin was added to the solution to aid in metabolizing some of the glucose. The decrease in plasma chloride was attributed to the loss in the vomitus, the daily excretion in the urine of 2 to 3 gm., and the redistribution in the body due to the glucose injection. The serum protein concentration slowly increased to normal, indicating that sufficient glucose had metabolized to permit protein formation instead of destruction.

We have made extensive studies of two other patients with oliguria and uremia after blood transfusions, and three with uremia due to renal pathology (one proved and one presumable cortical necrosis, and one nephrosclerosis). The blood and urinalyses were essentially the same in all cases. The first urinalysis, in all instances, showed very little solids, and the chloride and nonprotein nitrogen concentrations remained very low for a number of days. The increase in the amount of these substances was first due to the increased volume of urine. The concentration also increased eventually. The blood uric acid and creatinine began to decrease as soon as the urinary volume was 1,000 c.c. or more, but the blood nonprotein nitrogen did not begin to fall until the urinary excretion was 13 gm. or more.

When an oliguria or an anuria develops, the usual tendency is to give large amounts of water by mouth and by rectum. Water and electrolyte solutions are excellent diuretics, but they are usually contraindicated in patients with oliguria or anuria due to toxemia, blood transfusion reactions, etc., unless a chemical analysis reveals a deficiency. Physiologic salt and Ringer's solutions are of value in patients with a diminished urinary output due to dehydration and hemorrhage. Of course, blood is necessary when the true hemoglobin concentration is below normal.

In the treatment of oliguria and anuria, glucose, the normal sugar found in the blood, can be injected in large amounts without danger. The prolonged administration of hypertonic glucose solution in dogs will produce a hyperpyrexia, due to dehydration, but this requires several grams of glucose per kilogram of body weight over many hours. When glucose is injected intravenously in amounts beyond the ability of the body to store, burn, and excrete in the urine, the blood sugar becomes elevated to as much as 1,000 mg. per cent. During the period of hyperglycemia there is a compensatory decrease in the concentration of electrolytes and also a blood dilution. The composition of the blood is remarkably constant and is governed by its osmotic pressure. If the concentration of one substance is increased, an equivalent osmolar decrease occurs in another.

This mechanism is illustrated by the data in Table II. Five hundred cubic centimeters of a 20 per cent glucose solution were given intravenously to one of the authors (W. J. D.) over a period of thirty-one minutes. There was a decrease of 13 per cent in the cell volume and a decrease of 26 per cent in the serum protein concentration during the injection, indicating an increase in the plasma volume, and the return within one hour to their initial concentration. The interferometer measures exactly the concentration of all the solutes in the plasma and the figures reveal a decrease of 17 per cent during the injection and a rapid return to the original reading. The direction of change, that is, dilution or concentration, of the hemoglobin, cell volume and serum protein, has always been the same, but the actual percentage of alterations usually differs. Glucose is not an electrolyte and exerts, roughly, one-fifth of the osmotic pressure of sodium chloride, which accounts for the apparent discrepancy between the concentration of glucose and sodium chloride. However, if

TABLE II. CHANGES DUE TO THE ADMINISTRATION OF LARGE AMOUNTS OF HYPERTONIC GLUCOSE SOLUTION

Time in minutes	0	16	31	100
Plasma NaCl, mg. per cent	586	573	555	590
Plasma glucose, mg. per cent	97	450	550	159
Cell volume, per cent	48.5	44.0	42.0	48.0
Interferometer reading	1145	1009	949	1152
Serum protein, gm. per cent (interferometer)	7.4	6.1	5.5	7.3
Serum protein, Kjeldahl	7.4	6.1	5.4	7.4
Plasma CO ₂ , volume per cent	58	68	62	65
Nonprotein nitrogen	20	21	24	22
<i>Osmolar Equivalents—Calculated in mM.</i>				
Plasma NaCl	200	195.8	189.8	201.4
Plasma glucose	5.8	26.7	32.6	9.4
Plasma CO ₂	52.9	61.9	56.4	59.2
Serum protein	15.3	12.7	11.5	15.1
Nonprotein nitrogen	2.5	2.6	3.0	2.7
Inorganic P (estimated)	5.6	5.6	5.6	5.6
Lactic acid (estimated)	4.2	4.2	4.2	4.2
Total	286.3	309.5	303.1	297.8
<i>Osmolar Equivalents—Obtained</i>				
Freezing point lowering	0.544	0.560	1.532	0.546
Osmolar equivalents, mM.	294.0	302.7	287.6	294.6

one calculates the osmolar concentration of each substance, the increase of glucose is compensated for by a proportionate decrease in the electrolytes. Determinations of the freezing point illustrate how close the balance of the osmotic pressure is maintained. During the injection, a marked diuresis occurred and considerable amounts of chloride were excreted in the urine, as well as small amounts of glucose. We have made similar observations, with added conductivity measurements in three other patients.

Sunderman and Williams have confirmed our work. In their study they administered 75 gm. of glucose orally to diabetic patients, and found that the increase in the concentration of glucose in the serum, as moles per kilogram of water, was accompanied by a decrease in the concentration of chloride in the same units in approximately the ratio of 3.8 to 1. Our ratio is 2.7 to 1.

Sucrose and another carbohydrate, sorbitol, each of which, in a 50 per cent concentration and in amounts of 100 to 200 c.c., have been used individually as diuretics. The renal threshold for glucose is approximately 180 mg. per cent. The threshold for the above substances is zero. They require, theoretically, only one-half the osmotic adjustments in the plasma as does glucose, and if the kidney is functioning sufficiently to excrete these foreign sugars no harm will ensue. However, if the sucrose or sorbitol does not produce a secretion of urine, it remains in the blood stream and in the body and interferes with normal metabolism.

For example, an eclamptic patient was given 200 c.c. of a 50 per cent sucrose solution intravenously. The urinary output averaged 100 c.c. per hour, but the blood chlorides, which were 512 mg. per cent before the injection, were 244 mg. per cent four hours after the injection. The blood sugar at this time after hydrolysis was still 234 mg. per cent. A similar injection of sucrose was given, and the patient died one hour later.

We have given 200 c.c. of a 50 per cent sucrose solution to five other toxemic patients, and in all of them the depression of the plasma chlorides was greater and lasted longer than after the administration of glucose, despite the fact that the osmotic pressure of sucrose is one-half that of glucose. Such a prolonged and marked depression of the electrolyte concentration is dangerous to life, because it interferes with the normal metabolism of the erythrocyte and tissue cells. We have had no experience with sorbitol, but its action would be similar to that of sucrose. Furthermore, Lindberg, Wald, and Barker have demonstrated that an injection of sucrose in a dog resulted in albuminuria and hematuria, and that sections of the kidney showed changes ranging from scattered areas of hyperemia to actual hemorrhagic necrosis of the glomeruli and marked tubular degeneration. Therefore, if these foreign carbohydrates are administered, they should be used with caution, and then only to increase the output of urine from an already functioning kidney.

Acacia and gelatin solutions have been used to increase the blood volume, and acacia has been used by us to produce a diuresis. A number of fatalities have been reported following the injection of certain types of acacia solution. No report in the literature has included the manufacturer's name nor a description of the solution.

We studied one patient who died following an injection of a specially prepared electrolyte-free solution of acacia. The blood pressure decreased to the shock level, coma ensued, the urinary output was adequate, the blood became more concentrated, and the plasma fibrin, which was 0.69 per cent before the injection, was 0 per cent four hours later, and the blood failed to clot.

We know of a parallel case also resulting in death. The usual acacia solution is water-clear, but the solutions used in the above described cases were opalescent. We have recently studied a third patient who was given a commercially prepared solution of acacia, and about three hours later a blood transfusion was given. An oliguria resulted and, although the twenty-four-hour urinary output finally amounted to 2,500 c.c., the patient died, apparently from sepsis. Studdiford has reported several fatalities in which acacia was probably the cause. He does not mention the name of the manufacturer nor the type of solution used. We believe that acacia solution is indicated primarily in shock, and we would not hesitate to use a properly prepared solution if blood were not available.

A 4.3 per cent solution of sulphate has been injected intravenously in the treatment of anuria. We have mentioned our objections to electrolyte solutions where there is renal impairment.

CONCLUSIONS

Oliguria is defined by us as the excretion of less than 600 c.c. of urine within twenty-four hours, and anuria as the absence of urine for twelve or more hours. Either condition, if present, is a serious complication in patients with eclampsia and pre-eclampsia, dehydration, massive hemorrhages, and blood transfusion reactions.

Electrolyte solutions are indicated in patients with dehydration and massive hemorrhage, but are contraindicated in the other conditions.

Acacia, sucrose, and sorbitol solutions are contraindicated in patients with anuria or marked oliguria.

Intravenous injections of a 20 to a 50 per cent glucose solution in distilled water are ideal in the treatment of oliguria and anuria occurring in patients with eclampsia and pre-eclampsia, and after blood transfusion reactions.

Blood transfusion entails a mortality of 0.1 to 0.3 per cent. These deaths are presumably preventable if proper precautions are taken in the typing, matching, and transfusion of the blood.

Oliguria or anuria requires an early diagnosis and intensive treatment, because the longer the renal impairment is disregarded, the more difficult it is to promote a secretion of urine. The treatment comprises a carefully balanced intake and output. Chemical analyses of the blood for cell volume, nonprotein nitrogen and plasma chlorides are also of inestimable value as a guide in the treatment.

REFERENCES

- (1) *Baker, S., and Dodds, E.*: Brit. J. Exper. Path. 6: 247, 1925. (2) *Dieckmann, W. J.*: AM. J. OBST. & GYNEC. 31: 734, 1936. (3) *Idem*: Ibid. 22: 351, 1931. (4) *Dieckmann, W. J., and Crossen, R.*: Ibid. 14: 3, 1927. (5) *Dieckmann, W. J., and Daily, E. F.*: Ibid. 30: 1, 1935. (6) *Dieckmann, W. J., and Michel, H.*: Proc. Soc. Exper. Biol. & Med. 32: 1591, 1935. (7) *DeGowin, E. L.*: Ann. Int. Med. 11: 1777, 1938. (8) *DeGowin, E. L., Osterhagen, H., and Andersch, M.*: Arch. Int. Med. 59: 432, 1937. (9) *Drabkin, D., Wideman, A., and Landow, H.*: J. Biol. Chem. 27: 109, 1935. (10) *Goldring, W., and Graef, I.*: Arch. Int. Med. 58: 825, 1936. (11) *Lindberg, H., Wald, M., and Barker, H.*: Ibid. 63: 907, 1939. (12) *Schwarz, O., and Dieckmann, W. J.*: AM. J. OBST. & GYNEC. 18: 515, 1929. (13) *Studdiford, W.*: Surg. Gynec. Obst. 64: 772, 1937. (14) *Sunderman, F., and Williams, E.*: J. Clin. Investigation 14: 245, 1935.

DISCUSSION

DR. WILLIAM A. THOMAS (Abstract).—I have seen very few cases of anuria or oliguria which came from renal disease itself. Even in the most advanced disease where there is an inability to excrete solids we still may have a normal amount of urine. The criteria by which we determine renal damage are the failure of the kidneys to concentrate and to dilute. So in these cases we may still have a relatively correct amount of urine but the solids are low and the patient may go into uremia. On the other hand, in oliguria or a decreasing amount of urine with high specific gravity, we cannot possibly have renal damage. So with a specific gravity of 1.010 to 1.030 there is obviously no inability of the kidney to excrete solids. It is a lack of water for the kidneys.

The question of dehydration demands some consideration. Edema was recognized largely as a nonrenal condition. It is a condition in which there is an increased tissue thirst and increased movement of the metabolites into the tissues. There are two types of dehydration: one is simply a lack of water administered to the body, the other a loss of fluid from vomiting or diarrhea. This is not true dehydration. There is a clinical condition called dehydration which is the exact opposite of edema, the reverse movement of metabolites is present, and in this condition anuria is the end result. As these cases are examined, the tissues are dry and there is an inability to hold water. Whether you give water subcutaneously or intravenously, there is no absorption. It remains in the tissues in lumps or masses. When we talk about dehydration we must distinguish between these two. When dehydration is due to alkalosis and has been preceded by polyuria, we must give large quantities of salt and hydrochloric acid in an effort to make the patient edematous. The decreased renal output in oliguria and allied conditions is probably due to tissue disease; it is an inability to get water to the kidneys. The kidneys are not badly damaged. Recovery is prompt and restoration of function is rapid.

When Dr. Dieckmann says that the tissues are saturated with water and salt as long as there is oliguria or anuria, my belief is that the tissues are not saturated. They contain an excessive amount of water and salt and all of these materials are moving into the tissues, and consequently eventually a diuresis results.

The action of glucose obviously is to increase the osmotic pressure of the blood itself, which is frequently lowered by the loss of serum proteins and the loss of electrolytes. The lowering of this osmotic pressure is the result of more fluid going into the circulation than is absorbed. With hypertonic solution we get a temporary increase in osmotic pressure. I have never seen it measured as Dr. Dieckmann has shown. I agree with Dr. Dieckmann that it is a very dangerous procedure to give electrolytes in the presence of poor renal function. When they are retained in the body as foreign substances they frequently cause more trouble than the condition we are seeking to remedy. It is true in the toxemia of pregnancy, though we see it too in nephritics.

I am not sure about the filtration pressure of the urinary arterioles. It has been frequently said that when this pressure falls below 80 there is anuria. It seems to me that failure of the urinary secretion is not due so much to a lowered systolic pressure as it is to a diversion of the fluids in the tissues.

DR. W. J. DIECKMANN (closing).—I agree that glucose is not a panacea for all diseases. Other solutions must be used when indications arise for them. Whenever there is poor renal function, caution should be used in the administration of solutions containing electrolytes.

ENDOMETRIUM-LIKE MUCOSA LINING THE FALLOPIAN TUBE*

ITS ORIGIN, DIFFERENTIAL CHARACTERISTICS AND CLINICAL SIGNIFICANCE

ANDREW A. MARCHETTI, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York Hospital, Cornell University Medical College)

DEVELOPMENTAL abnormalities of the gross structure of the body, or its individual organs, so far as their form and function after maturity are concerned, invariably carry with them histologic, pathologic, and clinical factors of importance. Most of the gross defects in structure are well recognized and if not completely understood are at least familiar and their general implications can be evaluated. On the other hand, although they may or may not occur as frequently in the body as the grossly abnormal processes do, abnormal changes in cells or layers of cells are less often seen and are more difficult to understand. Furthermore, although tissue abnormalities do not always have the same pathologic and clinical import as gross changes unquestionably they must be regarded as biologically significant. The cellular and tissue changes that are concerned primarily with repair and regeneration, as well as those profound alterations in cellular architecture which are associated with tumor formation or those which Hanseman has designated as anaplasia, will be avoided in this consideration. To be more specific, the changes to which we wish to make particular reference are those designated as metaplasia and heteroplasia. The general patterns of these atypical cellular and

*Presented at a meeting of the New York Obstetrical Society, March 12, 1940.

The author wishes to express his thanks to Dr. Herbert F. Traut and Miss Alberta Kuder for the invaluable aid they so kindly offered in the preparation of this paper.

tissue transformations are familiar to almost all, but as has been stated there is need for a better understanding of them though there is general acceptance of a variety of influences and factors that are in operation to alter the normal pattern. Pre-eminently among these factors and influences, the vitamins, the hormones, and irritation due to infection have established significance unless further experimental and clinical investigation prove to the contrary.

Assuming that the current meaning of the two closely related terms metaplasia and heteroplasia is acceptable, instances can be multiplied in which squamous metaplasia has been demonstrated in the cervical canal, the uterine cavity and the tubal lumen. Mucous glands in the vagina, patches of gastric mucosa in the esophagus, and pancreatic tissue in the gastrointestinal tract may be mentioned as well-known examples of heteroplasia.

Since the female genital tract is an important part of the background upon which the subject of this paper is focused, it may be advisable for a better understanding of its development and versatility to recall that the embryonic relationship of the coelomic epithelium to that of the Müllerian duct is a very intimate one. It follows that actually the lining of practically the entire female genital tract descends from the same parent tissue, that is the Müllerian epithelium. The knowledge of this fact will later facilitate the explanation of why an atypical finding, though very rarely observed, should not be considered as particularly strange or inexplicable.

These introductory remarks now lead us to consider one of those abnormal tissue changes which is very infrequently seen and seldom described, that is, the complete or partial lining of the oviduct by a mucosa identical to that lining the uterine cavity, the endometrium. In the experience afforded by the laboratory of the New York Lying-In Hospital since 1932, there have been two instances in which the Fallopian tube was found to be lined by endometrium-like mucosa. The finding was so striking in each case that it was thought to merit study from the point of view of its origin, differential characteristics, and clinical significance. In surveying the literature, it was soon realized that little or nothing could be obtained from English sources and that for the most part the subject had been considered chiefly by the German writers. Further appraisal of what had been written revealed that a study of this abnormality would have little inherent clinical value. However, a review of the theories of origin in addition to the fact that the phenomenon probably represents another link in the chain of those interesting instances in which the morphology and function of cells and tissues presumably are transformed by the influences of vitamins, hormones or irritation, seems to place it outside the bounds of a bare histologic curiosity and, therefore, to justify this presentation.

One wishes to point out that the replacement of typical tubal mucosa by endometrium-like mucosa must not be confused with such pathologic lesions as endometriosis, adenomyosis of the tube, salpingitis isthmica nodosa, and follicular salpingitis, even though it is possible

that the abnormality may overlap or may be directly or indirectly related to any of them. Furthermore, one should like to divorce the process from the conception that it is ectopic endometrium as suggested by the theories of Novak and Sampson. On the contrary, it should be treated as Robert Meyer does, namely as a mutation which occurs locally in the tubal mucosa, capable of reacting to hormonal changes even to the point of menstrual desquamation just as uterine mucosa does.

A Fallopian tube lined by endometrium instead of tubal mucosa was first noted by Webster in his monograph on *Ectopic Pregnancy*, published in 1896. He made the observation on the opposite tube in a woman operated upon for ectopic pregnancy. Since then, further observations and case reports have been recorded by Höhne, Schridde

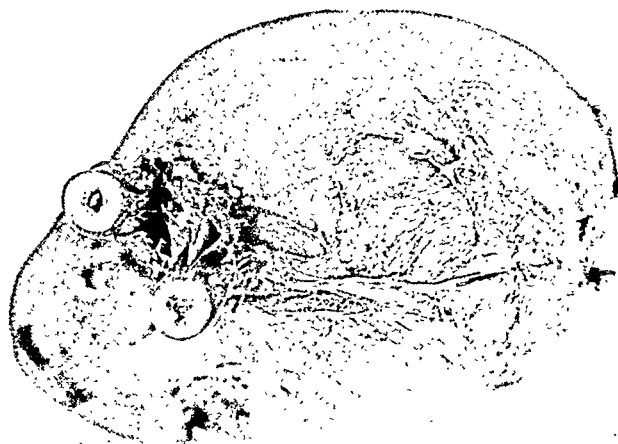


Fig. 1.—Case 1. Gross specimen illustrating the length and thickness of the affected Fallopian tube and the appearance of its cut surface.

and Schönholz, Schwarz and Crossen, Schindler, Mestitz, Lahm, Robert Meyer, Szamek, Cordua, Neumann, and most recently by Philipp and Huber. In this review and discussion, we wish to include the report of the two cases which came under our observation.

CASE 1.—A. T. (Hist. No. 164222), a married negress, aged 37 years, had one child aged 15 years, was admitted to this clinic April 5, 1937, complaining of lower back pain of two years' duration and worse at the time of her menstrual periods. She was told by her family physician that she had "fibroids." Her past history was essentially negative. Especially important are the facts that she had no operations nor any history of pre-existing pelvic infection. The only irregularity in her menstrual history was the experiencing of dysmenorrhea for the past two years, during the first three days of her periods. Last menstrual period was March 16.

Except for an enlarged nodular uterus, physical examination was essentially negative. On April 7, 1937, a subtotal hysteromyomectomy, right salpingo-oophorectomy, and appendectomy were performed. The left tube and ovary, which appeared normal, were allowed to remain in situ.

The postoperative course was uncomplicated and to date has been asymptomatic and satisfactory.

Pathology.—The specimen consisted of a myomatous uterus with the right tube and ovary attached to it, the ovary being about normal in size and appearance. The tube was 4 cm. long, of fibrous consistency, and the normal convolutions were found wanting. The distal half was thickened measuring about 1 cm. in



Fig. 2.—Case 1. Cross section of the Fallopian tube, demonstrating the endometrium-like mucosa lining the lumen. $\times 10$.



Fig. 3.—Case 1. A high power magnification of an area in the mucosa in Fig. 2, showing its similarity to the endometrium (see Fig. 4) and corresponding to the secretory phase. $\times 240$.

diameter at its widest portion, the fimbriated end was sealed and smooth. Anatomic relationships were accurately established to exclude the possibility of a rudimentary horn of a bicornuate uterus.

Microscopic examination of the uterine tumor revealed a typical myoma, undergoing hyaline degeneration. The ovary included a corpus luteum and was devoid of abnormal findings. The endometrium was in the secretory phase.

Cross section through the Fallopian tube taken at the point of maximum thickness showed the following striking changes: The serosal surface as a whole was intact and smooth. The muscular wall was thickened by a hyperplasia of the circular muscle fibers. The lumen was almost pear-shaped and lined by a mucosa identical to the endometrium. The glands, for the most part, were tortuous, lined by columnar epithelium with central to basal nuclei and the individual cells showed evidences of secretion. The glands were also embedded in a cellular connective tissue stroma whose cells were round to ovoid. There was a slight degree of leucocytic infiltration in the stroma. Thus the composition of this mucosa was not unlike that lining the uterine cavity and functionally demonstrated unmistakable hormonal response to the corpus luteum. The absence of any tendency to form mucosal folds was thought noteworthy. The line of demarcation between the mucosa and muscularis was regular and rather sharp.

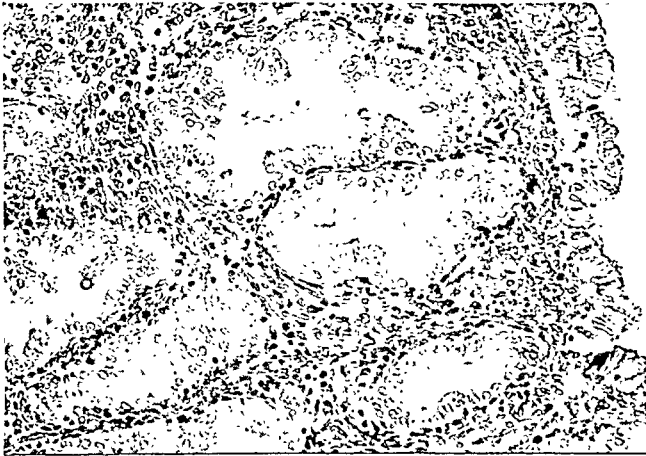


Fig. 4.—Case 1. A high power magnification of an area in the endometrium (uterus) in the secretory phase. $\times 240$.

Because of the findings in the routine section of the oviduct as described above, serial sections were cut for study and special stains to include examples from all parts of it. It was learned that the abnormality involved the distal half of the tube and that the proximal half showed the gradual transition and connection of the interstitial portion to the cornual portion of the endometrial cavity. Special care and interest were taken in this general area to exclude the presence of adenomyosis.

Diagnosis.—Myoma uteri, normal premenstrual endometrium, normal ovary with corpus luteum, normal appendix, Fallopian tube lined by endometrium-like mucosa (premenstrual phase).

CASE 2.—M. H. (Hist. No. 193773), a married white woman, aged 36 years, had one child aged 7 years, was admitted to the hospital Feb. 3, 1937, complaining of pain in the left lower quadrant of six months' duration. She had an attack of pain in the "left ovary" fifteen years ago, at which time she was confined to bed for a period of three weeks. There had been no irregularities in her menstrual history. Last menstrual period was Jan. 11, 1937.

Following routine physical examination, a laparotomy was advised for bilateral adnexal masses. On Feb. 3, 1937, the abdomen was opened. The uterus appeared normal. A multilocular cystic mass about 10 cm. was found in the region of the right ovary; a thick-walled cystic mass about 6 cm. in diameter replaced the left ovary. The uterus, both tubes and both ovarian masses, and the appendix were removed. Convalescence and follow-up were satisfactory.

Pathology.—The uterus was not remarkable. The capsules of both ovarian cystic structures were thick and the internal surfaces were covered by a thick chocolate colored hemorrhagic exudate. The left tube was 3.5 cm. long and about 0.75 cm. in diameter, the fimbriated end was sealed and smooth, no convolutions were

noted, the wall was fibrous in consistency. The right tube except for being roughened by adhesions appeared normal.

Microscopic examination revealed a normal myometrium and endometrium which was in the secretory phase. The sections of the ovarian cysts showed the characteristic evidences of endometriosis. Histologically the right tube was normal. A section through the left tube revealed a serosal surface whose regular and smooth contour was broken by adherent tags of organized connective tissue. The muscular layers were hyperplastic. The lumen of the tube tended to be rectangular in shape and was partially filled with a pinkish exudate containing a moderate amount of degenerated blood cells. The normal lining of the tubal lumen was replaced by an endometrium-like mucosa in the secretory phase. The histologic characteristics and details of this mucosa were like those described in the previous case. Once more serial sections were studied. The process in this Fallopian tube was found more extensive inasmuch as it involved the distal two-thirds of its length as compared to the distal half in the first case. Extension of the ovarian endometriosis to any part of the tubal wall was lacking, as well as any evidence of adenomyosis.

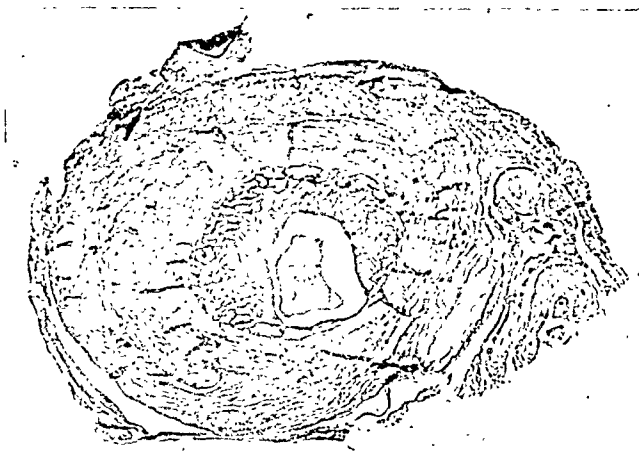


Fig. 5.—Case 2. Cross section illustrating the replacement of typical tubal mucosa by an endometrium-like mucosa in the secretory phase. $\times 10$.

Diagnosis.—Normal uterus with secretory endometrium, bilateral endometrial cysts of the ovaries, normal right tube, normal appendix, left tube lined by endometrium-like mucosa (secretory phase).

THEORIES OF ORIGIN

The thought advanced to explain the origin of this unique finding in the Fallopian tube may be divided into two general categories; one supports the theory that the abnormality is the result of a congenital anomaly, and the other builds its argument upon the presence of a congenital anlage from which a heteroplastic change may develop only after a stimulating factor has been released to react upon the anlage.

The writers who chiefly support a theory with a congenital anomaly as its background are Webster, Schriddé and Schönholz, and Schindler. Now, Neumann points out that there is a considerable difference between congenital anomaly and congenital anlage. In order that some abnormality or change can be considered a congenital anomaly, it must be present at birth, hence one should be able to see it in the fetus and in the newborn. Neumann pursued embryologic studies upon the course of the development of the Müllerian ducts up to the formation of the finished tube, and they failed to reveal the existence of any such mal-

formation, for he always found an open canal, never the rudiment of a diverticulum nor the fusion of tubal mucosal folds. The same negative results were realized when he completed a careful examination of 45 pairs of oviducts obtained from newborn full-term females. Robert Meyer's investigation of 300 Fallopian tubes likewise failed to show any congenital anomalies referable to the mucosa. It appears that the studies of Neumann and Meyer conclusively point to the fact that congenital malformations in the oviduct, according to the conception of Schridde and Schönholz, remain to be proved. Neumann is also of the opinion that the so-called "cytogene" or reticular tissue, to which Schridde and Schönholz refer, belongs to the normal course of development of the tubes, and with Lahm is agreed that it bears no relationship whatever to the "cytogene" tissue or stroma in the endometrium of the adult woman, and consequently cannot be offered as proof to uphold Schridde and Schönholz' theory of dysontogenesis.

Lahm believes in a congenital change but only in the sense that it is the outcome of a congenital lack of differentiation of the tubal mucosa whose source is a congenital anlage. The unfolding of this process into atypical mucosa, he proposes, is primarily dependent upon a particular stimulus, and the stimulus is initiated by the impulse of the ovarian hormones in the sexually mature woman. He definitely feels that the abnormality is not the result of an inflammatory process.

Robert Meyer attributes the finding of endometrium-like mucosa in the tube to heteroplasia. He feels that one should not wonder at such an intricate misplaced tissue differentiation in the oviduct when one stops to consider the fact that the lining of practically the entire female genital tract is derived from the Müllerian epithelium. He states boldly that it would be a distinct source of wonderment if endometrium could not be formed on the tube. It is reasonable to suppose then that there are especially suited cells lining the tubal lumen which may undergo misplaced differentiation, in other words, a congenital anlage lending itself to heteroplasia and indicating that the cell or group of cells constituting it is in possession of a dormant multipotent biologic capacity. Such indifferent cells must be aroused to development or proliferation as soon as they are affected by stimulus-releasing factors. When these particular cells give expression to their dormant capacity, it is clear that they can become an efficient functioning mucosa like the endometrium only in the presence of normal ovarian function. While Meyer believes that there is no unusual mucosal structure in the tube that inflammation cannot reproduce, it seems plausible to infer that the particular finding presented in this discussion can occur without having been preceded or initiated by an inflammatory process.

In the light of what has been advanced, there is sufficient evidence to make it appear that endometrium-like mucosa in the tube is unquestionably of postfetal origin and not the result of a congenital anomaly. Furthermore, Robert Meyer's theory of heteroplasia explains better than any other the process of its development, irrespective of the nature of the stimulus that initiates it.

DIFFERENTIAL CHARACTERISTICS

From the small number of cases that have been reported in the literature, it is clear that endometrium-like mucosa can exist in the tube without an associated lesion, such as salpingitis isthmica nodosa, adenomyosis, endometriosis, or follicular salpingitis. These pathologic processes are particularly mentioned because, at times, they may overlap or may even be confused with the atypical mucosal finding in the tube. For the purpose of contrast, it will be necessary to present

briefly the histologic picture and characteristics of the tubal abnormality, and then make some short comment as it is compared to the other lesions.

From the examination of the two specimens reported in this presentation, in addition to the others described in the literature, in general one may say that the Fallopian tube is usually thickened, may or may not have a bulbous enlargement along its course, is devoid of convolutions, the fimbriated end is usually sealed and smooth, and the altered mucosa may line the entire length of the lumen or only a part of it. Microscopically, the mucosa is found to be identical to the endometrium, and the ovarian hormones influence the function of the mucosa as if it were in the uterine cavity. The line of demarcation between the mucosa and muscularis is rather sharp and regular. The circular layer of muscle fibers, as well as the longitudinal, may be hyperplastic. Serial sections in our cases failed to reveal any epithelial spaces in the outer and middle layers of the musculature. Finally, any attempt on the part of the mucosa to form folds is not in evidence.

For comparison, let us first consider salpingitis isthmica nodosa and follicular salpingitis. It is generally agreed that the responsible agent for these lesions is always an inflammatory one, most frequently the gonococcus. One only needs to recall the pathologic picture of these two lesions, and by comparison it will be concluded that they bear no relationship to the tubal abnormality under consideration.

A pathologic process in many respects not unlike salpingitis isthmica nodosa, but which has nothing to do with it, is adenomyosis of the tube. It is a lesion which appears in the sexually mature woman and is characterized by nodular thickening only in the isthmic and interstitial portions of the tube. It is an example of heterotopic infiltrative proliferation of the mucosa, but unlike salpingitis isthmica nodosa occurs without proved pre-existing inflammation. This, without proved inflammation, must originate under conditions similar to its occurrence in the uterus. Two possibilities are offered for its origin in the tube: (1) transmission or continuation of uterine adenomyosis, (2) heteroplasia according to the theory of Robert Meyer. If one considers the second genesis, it is remotely possible that endometrium-like mucosa in the tube could be a forerunner of tubal adenomyosis.

Two points of special interest may be deliberated when endometrial mucosa in the tube is treated in relation to endometriosis. That it is a consequence of endometriosis is conceivable only so far as it is found in association with it in the sense that the stimulus which would cause the endometriotic process elsewhere, be it hormonal or inflammatory or both, might be the same factor responsible for the formation of the atypical mucosa in the tube. That it may be the cause of endometriosis in the pelvis has already been considered by Schindler and more recently by Philipp and Huber. If, according to their conception, such a membrane in the tube functions as in the uterus, then it seems reasonable to suppose that viable fragments could find their way through

the tubal lumen into the peritoneal cavity and there implant themselves to be the origin of endometriosis.

CLINICAL SIGNIFICANCE

Any conclusive or generalized statements relative to its clinical significance are prohibited because the cases are too few and the abnormality too rarely observed. However, most authors are in agreement that it may predispose the woman to ectopic pregnancy. Another consequence may be the development of a hematosalpinx as a result of tubal menstruation (cases of Lahm, Neumann, Meyer and Schindler). Should a hematosalpinx develop, it may become sufficiently symptomatic to be the cause of a real dysmenorrhea, as the cases of Meyer and Schindler clearly demonstrated. Finally, it is conceivable that the tubes bearing this abnormality may dispose the individual to sterility, since the fimbriated ends are usually sealed.

SUMMARY

1. The formation of endometrium-like mucosa in the Fallopian tube is a tissue abnormality which is infrequently seen and seldom described. It responds to the ovarian hormones in its functional activity, just as the endometrium does even to the point of menstrual desquamation.

2. Two cases with clinical and histopathologic findings are reported.

3. The theories of origin are briefly reviewed, and it is concluded that Robert Meyer's theory of heteroplasia explains better than any other the process of its development.

4. The differential characteristics are enumerated and contrasted with several pathologic lesions of the tube.

5. Endometrium-like mucosa in the tube carries little clinical value. Interest centers chiefly upon its biologic significance.

REFERENCES

- Cordua, R.*: Zentralbl. f. Gynäk. 52: 2371, 1928. *Hochne*: Ibid. 48: 233, 1924. *Lahm, W.*: Deutsche med. Wchnschr. 53: 1900, 1927. *Idem*: Arch. f. Gynäk. 130: 152, 1927. *Mestitz, W.*: Ibid. 131: 166, 1927. *Meyer, R.*: Zentralbl. f. Gynäk. 51: 1482, 1927. *Idem*: Veit-Stoeckel, Handb. der Gynäk. 6: 367, 1930. *Neumann, H. O.*: Ztschr. f. Geburtsh. u. Gynäk. 95: 437, 1929. *Idem*: Arch. f. Gynäk. 139: 358, 1930. *Novak, E.*: AM. J. OBST. & GYNEC. 12: 484, 1926. *Philipp and Huber*: Zentralbl. f. Gynäk. 63: 7, 1939. *Schindler, B.*: Ibid. 49: 582, 1925. *Schönholz, L.*: Ztschr. f. Geburtsh. u. Gynäk. 87: 56, 1924. *Schridde and Schönholz*: Frankfurt. Ztschr. f. Path. 30: 339, 1924. *Schwarz and Crossen*: AM. J. OBST. & GYNEC. 7: 505, 1924. *Szamek, L.*: Zentralbl. f. Gynäk. 52: 812, 1928. *Nürnberg, L.*: Veit-Stoeckel, Handb. der Gynäk. 7: 632, 1932. *Webster*: Die ektopische Schwangerschaft, Berlin, 1896, S. Karger.

DISCUSSION

DR. MORRIS A. GOLDBERGER.—The epithelium of the Fallopian tube may be the origin of this displaced or misplaced endometrium. This may be either pre- or postnatal. The postnatal origin is probably on the basis of inflammation with its concomitant proliferation and heterotopy. The epithelium of the uterus can invade the tubal wall by direct extension from the uterine cavity, or, according to Sampson, it may be transported in the course of retrograde menstruation with implantation in the tubal wall. Also, according to Sampson, rupture of an endometrial cyst with secondary invasion into the tube, may occur such as Dr. Marchetti noted in his second case.

Lymphogenic transportation of endometrium into the tube (Halban's theory) is not generally accepted, because endometrial tissue is never found in the regional glands and the endometrial particles are usually larger than the lymph stream can carry.

The seroepithelial genesis of endometriosis can occur by proliferation of serosal endothelium into the tube wall. We know that the pelvic serosal cells can respond to decidual changes.

Congenital epithelial anomalies may arise from Mueller's ducts, from the Wolffian body, or primordial kidney. This is stressed by von Recklinghausen, who found glomerular-like and secretory ductlike formations in the endometrium of the tube. The Wolffian duct and serosal endothelium have also been cited in fetal endometriosis.

These theories throw some light on the epithelial component, but there are still the stroma and the muscular elements, the origin of which, even hypothetically, is unknown. Sampson's theory, which is the most accepted one today, does not explain the formation of the cytogenic stroma in endometriosis. We know that epithelium can be transported or transplanted experimentally, but the stroma cells are very perishable and undergo rapid necrobiosis. This is commonly seen in menstrual endometrial casts.

It may be assumed that the cytogenic tissue in uterine endometriosis arises in the uterine mucosa. In tubal endometriosis, it may be the tubal mucosa or the intermuscular connective tissue which forms the cellular mantle in which the epithelial cells lie. This twofold origin of the stroma in endometriosis might explain some of the histologic pictures, because there are instances in which there is typical cytogenic stroma, and others in which a fibrillar connective tissue surrounds the epithelium and glands.

DR. ELIOT BISHOP.—The presence of endometrium-like mucosa in the Fallopian tube is connected in my belief with the occurrence of pregnancy after tubal ligation. Lutz, of the Peck Memorial Hospital in Brooklyn, has reported a case of ectopic pregnancy following the Madlener operation. Rubovitz and Kobac (*American Journal of Obstetrics and Gynecology* 27: 12, 1934) reported two cases of pregnancy after the original Madlener technique. Their sections seemed to show that there was tunneling of the endosalpinx which had probably undergone endometrial changes. Sampson (*American Journal of Obstetrics and Gynecology* 20: 443, 1930) has described "post-salpingectomy endosalpingiosis." This explains the rare cases of pregnancy after an operation on the Fallopian tube.

DR. HERBERT F. TRAUT.—The embryologic origin of all the epithelia of the female genital tract is identical in that they originate from celomic epithelium. Through occasional lack of differentiation or because of abnormal stimuli during periods of differentiation, we get histologic admixtures of apparently misplaced epithelial cells. Thus, we commonly see squamous changes among the cylindrical cells of the cervical glands as well as among those of the endometrium. Mucous cells similar to those of the cervix are sometimes found in the endometrium. On the other hand, it is not uncommon to find the peritoneum of the pelvis forming cells which simulate those of the endometrium and endosalpinx. This demonstration of Dr. Marchetti in which he definitely shows that the endosalpingeal epithelium may occasionally differentiate in the direction of endometrial mucosa instead of the usual type, while not of great clinical significance, is of importance, because it shows that all parts of the genital tract can undergo these mutations.

DR. WILLIAM LATZKO (by invitation).—I shall discuss only one feature of Dr. Marchetti's paper, namely, the manner in which the endometrium finds its way into the tube. The most generally accepted theories are:

1. R. Meyer's theory of heteroplasia, by abnormal differentiation of indifferent cells or of not yet fully differentiated cells;
2. The metaplastic theory of postfetal change of the mucosa of the Fallopian tube to endometrium.

My remarks will refer chiefly to the last mentioned theory. Caffier and others have doubted the possibility of metaplastic change of totally differentiated cells. Yet certain observations show us that Caffier's objections are not essential: (a) We find an extraordinary instability and variability of the endometrium at the time of puberty. (b) Furthermore, the endometrium and mucosa of the tube are both derivatives of the same tissue, namely the celom, as Russel pointed out as early as the year 1899. (c) Finally several authors (Franqué, Mahle and McCarthy, Lemon and Mahle, Sampson) have asserted that endometrioma of the tubes originates from the tubal mucosa. (d) It is interesting also to recall a most interesting communication of Morau who, in 1891, observed in the pig, dog, cat, and mouse the transformation of the peritoneal epithelium under the influence of rut first into embryonal, afterwards into ciliated, epithelium. In conclusion, it may be definitely stated that tissue descending from the celom is able to change its character in postfetal life. We may ask therefore why it is so difficult to suppose a postfetal transformation of tubal mucosa to endometrium.

There exists also, however, a real proof of metaplasia. I refer to clinical experiences with an operation described by Strassmann for cases of amenorrhea due to total or almost total loss of endometrium as a result of excessive curettage, severe puerperal infection or tuberculosis of the uterus. In this operation Strassmann made a hole through the uterus in the direction of its axis and introduced a tube, left in connection with the broad ligament, into the new formed uterine canal. Now the tube lay with its ampullar extremity opening into the peritoneal cavity and the uterine end projecting into the vagina. Strassmann performed that ingenious operation six times. With a similar operative technique devised to avoid amenorrhea after subtotal hysterectomy, Fuchs operated seven times. In these 13 patients regular menstruation continued. Moreover one of Strassmann's patients became pregnant and gave birth at full term to a normal child. That proves almost with certainty that the Fallopian tube can assume such functions of the uterus as menstruation, formation of decidua, and support of pregnancy to its normal termination. So we can state with a probability near to certainty, that in these cases the tubal mucosa was changed into endometrium.

PROLAPSE OF THE UMBILICAL CORD*

AN ANALYSIS OF 58 CASES

WILLIAM F. MENGERT, M.D., AND FREEMAN H. LONGWELL, M.D.,
IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, The State University of Iowa)

PROLAPSE of the umbilical cord is an infrequent complication of labor, which becomes significant because of the resultant high fetal mortality rate and the employment of radial operative procedures that increase the maternal hazard. Little is known about its etiology except that conditions which interfere with the proper filling of the pelvic cavity by the presenting part conduce to its development. This study was undertaken to ascertain whether any other factor, possibly nonpreventable in character, could be recognized as favoring funic prolapse.

MATERIAL

Among 9,546 deliveries at the University Hospitals between July 1, 1926, and Dec. 31, 1939, there were 63 prolapsed cords, an incidence of 1:152, or 0.66 per

*Presented at a meeting of the Chicago Gynecological Society, March 15, 1940.

cent. Five cases involving previable infants (birth weight less than 1,500 Gm.) were excluded from the analysis, making a corrected incidence of 1:164, or 0.61 per cent. Forty-nine of the children weighed 2,500 or more grams at birth and 9 weighed between 1,500 and 2,499 Gm. Twenty cords prolapsed into the vagina and 38 appeared at the vulva.

The series included 23 primigravidas and 35 multigravidas whose obstetric histories presented no unusual features and no records of similar accidents. Abnormal pelves (simple flat, 1; typical funnel, 3) were recognized in 4 women, an incidence of 6.9 per cent. There were 2 twin pregnancies, but in each instance the cord of the second child did not prolapse. There were 2 marginal placenta previas and 5 toxemias of late pregnancy, necessitating the induction of labor. Three children showed compound presentations, in contrast to the usual incidence of approximately 1:250.

The Voorhees bag was used 7 times, twice in conjunction with the cord shield, 3 times in attempts to maintain the cord within the uterine cavity after replacement, and twice for incidental obstetric complications. Artificial rupture of membranes was performed 21 times, in 14 instances for the induction of labor and in 7 after complete cervical dilatation.

MORTALITY RATES

Twenty-seven of the 58 babies did not survive, a mortality rate of 46.6 per cent. Among the 49 term babies there were 20 deaths (40.8 per cent) and among the 9 premature infants 7 deaths (77.7 per cent). Four patients were admitted with prolapsed cords, but none of the children survived, although 2 of the cords were pulsating feebly at admission.

The 27 fetal deaths were studied with relation to the parity of the mother, the station of the presenting part, the dilatation of the cervix at the time of prolapse, the fetal presentation, and the type of delivery.

Parity.—The fetal mortality rate among the primigravidas was 60.9 per cent and among the multigravidas 37.2 per cent. The higher rate in the former is undoubtedly related to the longer labors and to the greater difficulty of operative deliveries.

Station.—As might be expected, the higher stations of the head were associated with increased fetal mortality rates (Table I). When the presenting part was not engaged, or floating, the death risk was 75 per cent greater (66.6 per cent) than when the presenting part was below the spines (37.5 per cent).

TABLE I. FETAL MORTALITY RATES VERSUS STATION OF PRESENTING PART AT THE TIME OF PROLAPSE

	CEPHALIC		BREECH		TRANSVERSE		TOTAL		
	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	PER CENT
Not engaged	2	3	0	2	2	3	4	8	66.6
At or above the spines	9	10	8	3	—	—	17	13	43.4
Below spines	6	4	4	2	—	—	10	6	37.5

Note the decrease in fetal mortality rate with the descent of the presenting part in the pelvis.

Cervical Dilatation.—The chance for fetal survival was also diminished when the prolapse occurred through an incompletely dilated cervix (Table II). With complete cervical dilatation, the fetal mortality rate (36.7 per cent) was not quite 60 per cent as great as when the cervix was less than 5 cm. dilated (63.8 per cent).

Presentation.—Fetal position likewise influenced fetal survival, with the lowest death rate in breech and the highest in transverse presentations. It is curious, as Kurzrock¹ has indicated, that the fetal death rate is relatively high in transverse presentations where the possibility of serious cord compression would seem to be minimal. Possibly the fact that in such cases the cord prolapses through an incompletely dilated cervix and that rapid delivery by version and extraction is commonly employed may explain the poor results.

TABLE II. FETAL DEATH VERSUS DILATATION OF CERVIX AT THE TIME OF PROLAPSE
FETAL DEATH VERSUS PRESENTATION

	CEPHALIC		BREECH		TRANSVERSE		TOTAL		
	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	
								NO.	PER CENT
5 cm. or less	3	6	1	4	1	1	5	11	63.8
More than 5 to 10 cm.	2	3	4	1	1	1	7	5	41.7
10 cm. or more	12	8	7	2	0	1	19	11	36.7
Totals	17	17	12	7	2	3	31	27	46.6

Note the decrease in fetal mortality rate with the increase in size of the cervix.

ETIOLOGY

Many theories concerning the etiology of funic prolapse have been advanced, but none offers a completely satisfying explanation. Since no cord can prolapse into a pelvis which is adequately filled by the presenting part, nor descend from an intact amniotic sac, any circumstance which: (1) produces maladaptation of the presenting part to the pelvis (malposition of baby, contracted pelvis, tumors, etc.), (2) dislodges an engaged presenting part (insertion of bag, pelvic examination), or (3) produces early rupture of membranes, has been considered etiologically significant. Moreover, a few authors have suggested that the chance occurrence of an abnormally long funis may be important. Each of these theories will be discussed.

Maladaptation.—With a normal pelvis and a normal size baby, an engaged head should fill the available space in the pelvic basin, whereas a breech would fill it less completely. With transverse presentations, on the other hand, the baby does not adapt itself to the pelvis until comparatively late in labor. In confirmation of these opinions there were prolapsed cords in 34 of 9,092 cephalic, 19 of 419 breech, and 5 of 35 transverse presentations, with percentage incidences of 0.37, 4.54, and 14.27, respectively.

In the present series there were 4 (6.9 per cent) contracted pelves, as against an incidence of 3.65 per cent in 4,144 Iowa women.² However, there was but one inlet contraction, and funnel pelvis is probably not involved in the etiology of prolapsed funis.

Dislodgment of Presenting Part.—Upward displacement of the presenting part may occur during the conduct of labor, as in the introduction of a Voorhees bag or at premature rupture of the membranes, and may precipitate funic prolapse. The bag was employed twice for incidental obstetric complications, placenta previa and delayed cervical dilatation, and in each instance the cord prolapsed as soon as the bag was removed. On the other hand, the bag is frequently employed without the occurrence of prolapse. Moreover, the accident occurred in five cases immediately after the artificial rupture of the bag of waters.

Rupture of the Membranes.—Prolapse of the cord cannot occur with an intact amniotic sac, even though funic presentations may appear before the membranes are ruptured and thus predispose to prolapse. Except in these latter cases, it is not reasonable to assume that rupture of the bag of waters is the sole cause of prolapse of the cord even though it does immediately precede the accident. In 14 cases, premature artificial rupture of the membranes preceded the prolapse. In 5 instances, the cord prolapsed immediately, while in the remaining 9 cases, the prolapse occurred from fifty minutes to thirteen hours later, suggesting the operation of some other factor.

These figures are confusing, but a study of 1,000 women in whom labor was induced electively by premature artificial rupture of the membranes³ showed only 4 prolapsed cords, while a control series of 1,000 women who had spontaneous onset

of labor without artificial rupture of membranes also had 4 prolapsed cords. The first group was carefully selected with regard to bony pelvis and presentation to reduce the possibility of prolapsed cord. Nevertheless it is apparent that the complication should have appeared much more often if premature artificial rupture of the membranes is a significant factor in the etiology of prolapse of the funis.

Long Cord.—Since a prolapsed cord is *doubled* it must be of considerable length before the loop can appear at the vulva. The average length of 55 measured prolapsed cords was 73.0 cm. (Table III). Three cords were not measured. Since the accepted range of normal cord length is 25 to 75 cm., it is apparent that the average length of the 55 prolapsing cords was at the extreme upper limit of normal. It is felt that chance alone could not account for this finding.

Apparently prematurity was not a factor influencing cord length, since there was no significant difference between the average cord lengths of premature and of term-sized babies (Table III).

TABLE III. DISTRIBUTION AND AVERAGE OF PROLAPSED CORDS

CENTIMETERS	TERM NO.	PREMATURE NO.	TOTALS NO.
45-49	2	0	2
50-59	3	1	4
60-69	11	4	15
70-79	14	2	16
80-89	12	0	12
90-99	3	1	4
100-109	1	1	2
Totals	46	9	55
Average Length	73.2 cm.	72.1 cm.	73.0 cm.

The lengths of the cords less than 60 cm. were: 45, 49, 50, 56, 56, 57.

Note that prolapsing cords tend to have an average length at the extreme upper limit of normal, and that there is no significant difference between the average lengths of cords of term and of premature babies.

The average cord length of the 5 abortions was 62.0 cm.

Only 6 prolapsed cords were less than 60 cm. in length. A detailed analysis of these cases was undertaken to ascertain if there were any special features contributing to the prolapse. In 4 the funis prolapsed into the vagina but did not appear externally, possibly because the cord was not sufficiently long. There was no evidence in any of the 6 to indicate that low placental implantation contributed to increase of the effective cord length but the possibility cannot be eliminated. No other etiologic factor was revealed.

Believing that abnormal cord length may play a more important part in causing prolapse of the funis than has generally been recognized, an analysis of patients with prolapsing as well as those with nonprolapsing cords 75 or more centimeters long was undertaken. There were 545 such umbilical cords of which 20 prolapsed and 525 did not.

The influence of the long cord is shown in Table IV. If, in addition to recognized etiologic factors, a long cord is present, the danger of prolapse of the funis is strikingly increased. Prolapse among the long cords occurred with a frequency 6 times greater than that among the entire series of 9,546 deliveries. This suggests that the long cord is a definite and important factor in the etiology of prolapse of the funis.

While the danger of funic prolapse is moderate when there is maladaptation of the presenting part to the pelvic inlet, as in breech and transverse, it is much greater when the umbilical cord is 75 or more centimeters in length. As a corollary, one may assume that the danger of a funic prolapse in breech and transverse presentations is comparatively slight if the cord is of average length, but becomes increasingly serious with longer cords.

Nonprolapsing Long Cords.—In order to determine the probable reasons for the failure of prolapse of the 525 long cords each of the case records was analyzed.

TABLE IV. INCIDENCE OF PROLAPSE, IN GENERAL AND AMONG PATIENTS WITH CORDS MEASURING 75 OR MORE CENTIMETERS

	ENTIRE OBSTETRIC SERVICE			PATIENTS WITH LONG CORDS		
	DELIVERIES	PROLAPSE OF FUNIS		DELIVERIES	PROLAPSE OF FUNIS	
	NO.	NO.	PER CENT	NO.	NO.	PER CENT
Cephalic	9092	34	0.37	509	9	1.8
Breech	419	19	4.54	33	9	37.5
Transverse	35	5	14.27	3	2	66.6
Totals	9546	58	0.61	545	20	3.7

Note the striking increase in the percentage incidence of prolapse in each position with long cord.

The frequency of prolapse among patients with long cords was 6 times greater than among the entire obstetric service.

Between July 1, 1926 and Dec. 31, 1937 among 7,874 women, there were 525 instances of nonprolapsing cords, measuring 75 or more centimeters. The incidence of long cord without prolapse was, therefore, 6.17 per cent, or 1:15. Repetition of the long cord was observed twice in 18 women, three times in 4, and five times in 1.

There were 500 cephalic, 24 breech, and 1 transverse presentations in this series. There was no patient with inlet contraction, so that the presenting part was free to enter the pelvis in each instance. The usual factors influencing prolapse, notably maladaptation, were conspicuously absent. Furthermore, in complete or single footling breech presentations where prolapse might commonly be expected, adventitious factors, such as coils of cord around the neck, tended to prevent it.

It seems reasonable to assume that maladaptation of the presenting part to the pelvis was absent in the 500 vertex presentations in this series. In other words, the cord could not enter a completely full pelvis. Seventeen of the 24 breech presentations were of the frank variety and again an adequate filling of the pelvic inlet may be postulated. In each of the 3 patients with complete breech, and in 3 of 4 single footling presentations, the cord encircled the baby's neck one or more times. In the fourth single footling presentation, labor was precipitate, lasting only thirty-five minutes from onset until the legs and breech were born. It can be argued that with a longer labor, prolapse of the funis might have been encountered. In the one instance of transverse presentation, an arm prolapsed when the cervix was 3 cm. dilated, and it may be there was no room for the cord between arm and cervix.

It seems possible, therefore, to find a more or less adequate explanation for the failure of the long cord to prolapse in each of these 525 instances.

THERAPY

It is essential to remember that treatment for prolapsed cord is of importance only if the baby is alive. A physician recently brought a parturient primigravida to the Hospital with the story that a foot of a pulseless loop of cord had been hanging between her thighs for some hours. He was greatly disturbed when cesarean section was not performed.

Whenever the station of the presenting part and the condition of the cervix permit, immediate vaginal delivery is indicated. It must, however, be remembered that the child may die, not as a result of the prolapse, but from the operative procedure itself (Table V).

If conditions will not permit vaginal delivery without undue risk to the mother, recourse may be had to: (1) replacement, (2) the cord shield, (3) cesarean section, (4) acceptance of an unfortunate circumstance.

Replacement of the cord was attempted 4 times but could be accomplished only twice. One of these patients was a gravida xi whose cervix was half dilated. It

became sufficiently dilated during the vaginal manipulations to permit breech extraction of a living baby. The other unsuccessful attempt involved a gravida i whose cervix was half dilated when prolapse occurred and the baby subsequently was spontaneously stillborn. The cord was replaced and a bag inserted into two patients, both of whose babies were lost. It is of interest that the various operators avoided the use of replacement, since it was attempted but 4 times.

TABLE V. ASSOCIATION OF TYPE OF DELIVERY WITH FETAL DEATH

	ALIVE NO.	DEAD	
		NO.	PER CENT
Craniotomy	0	1	100.0
Cesarean section	0	1	100.0
Low forceps	4	6	60.0
Midforceps	3	3	50.0
Breech extraction	12	9	42.8
Spontaneous delivery	3	2	40.0
Version and extraction	8	5	38.5
External version, breech extraction, manual dilatation	1	0	00.0
Total	31	27	46.0

Note that despite the known danger of version and extraction to the fetus, the operation sometimes was a life-saving measure.

Certainly the results were not good, and are in agreement with common teaching that replacement is little more than a gesture.

The cord shield was used twice, each time with fatal results to the baby. In the first case, previously reported,⁴ the baby died from intracranial hemorrhage four hours and twenty minutes after breech extraction. The second patient was admitted with a pulsating cord prolapsed through a cervix 2 cm. dilated. The baby died in utero, but it is felt that with more experience in the use of the shield it might have been saved. Despite these poor results the shield may be of some value.

Cesarean section was not generally used, since it has not been considered justifiable to expose the mother to increased risk for a baby whose chances are so poor. The operation was performed once on a gravida iii at term, but not in labor. The cervix was 2 cm. dilated and the fetal heart was heard before the patient's abdomen was prepared. The baby, weighing 2,745 Gm., could not be resuscitated, and it was thought that the addition of an anesthetic agent to a partially asphyxiated baby was a fatal combination.

It is sometimes advisable for the sake of the mother to allow labor to progress normally without regard for the child. Especially when the cord has been compressed for a long time there is little justification for any radical operative attack.

Many bizarre and sometimes ludicrous incidents attended the deliveries. Under the pressure of circumstances absurd operations frequently were performed, sometimes with failure, sometimes with success. As a specific example, the baby of a gravida iii with a cervix 4 cm. dilated at the time of prolapse was saved by external version, manual dilatation and breech extraction. In another instance a gravida iv who was subjected to premature artificial rupture of the membranes when the cervix was 3 cm. dilated immediately pushed a loop of nonpulsating cord through the cervix. The fetal heart was audible and the patient was placed in an extreme Trendelenburg position. When labor started eighteen hours later the cord prolapsed to the vulva. Before and during the subsequent labor, which lasted three-and-one-fourth hours, the patient remained in extreme Trendelenburg position. When the cervix was 8 cm. dilated, version and extraction resulted in the birth of a 3,800 Gm. living baby. In one of the instances of prolapse with premature artificial rupture of the membranes, the patient was placed in extreme Trendelenburg position and anesthetized. The cord returned spontaneously to the uterine cavity and subsequently the head re-entered the pelvis. The cord did not prolapse again and a live baby was born spontaneously. Undue enthusiasm over two successes is not justifiable, but postural treatment may occasionally be of value.

SUMMARY AND CONCLUSIONS

1. Prolapse of the umbilical cord in the series of cases studied, occurred in 0.61 per cent of babies weighing 1,500 or more grams at birth, an incidence of 1:164.

2. The percentage incidence of prolapse among the various presentations was: cephalic 0.37, breech 4.54, transverse 14.27.

3. The fetal mortality rate was 46.6 per cent, but no mothers died.

4. The death rate of babies of primigravidas was almost twice that of babies of multigravidas.

5. The station of the presenting part at the time of prolapse influenced the fetal mortality rate as follows: at inlet 66.6 per cent, at mid-pelvis 43.4, at outlet 37.5.

6. The condition of the cervix at the time of prolapse influenced the fetal mortality rate as follows: Less than 5 cm. dilated 63.8 per cent, between 5 and 10 cm. 41.7, complete dilatation 36.7.

7. Premature artificial rupture of the membranes for the elective induction of labor did not influence the incidence of prolapse of the funis.

8. The average length of the prolapsed cords was 73.0 cm.

9. Among 545 patients with cords 75 or more centimeters long prolapse occurred with a frequency 6 times greater than among the entire obstetric service.

10. The chance occurrence of a long cord is a prominent factor in the etiology of prolapse of the funis.

11. Treatment is inadequate. It is stressed that: (1) It is important only if the baby is alive, (2) undue jeopardy of the mother is not justifiable in view of the poor fetal prognosis.

REFERENCES

(1) Kurzrock, Julius: AM. J. OBST. & GYN. 23: 403, 1932. (2) Mengert, William F.: Ibid. 36: 260, 1938. (3) Keettel, W. C., Diddle, A. W., and Plass, E. D.: 40: 1940. (4) Mengert, William F.: AM. J. OBST. & GYN. 31: 153, 1936.

DISCUSSION

DR. DAVID S. HILLIS.—It appears from the comparison of Dr. Mengert's figures with the record of the Cook County Hospital that this accident occurs more frequently in Iowa than it does in Illinois. At the Cook County Hospital in 9,581 deliveries of viable infants, prolapse of the cord occurred only 25 times. Three patients were admitted with prolapsed cord in which the baby was already dead, so that if these be excluded from our series 22 cases are left to be considered. The total mortality among these cases was three babies, i.e., 13.6 per cent. One fetal death occurred in a primigravida and two in multigravidas. In 20 cases the pelvis was normal, in one case it was contracted, and in one case it was a justomajor pelvis. There were 11 breech cases, 10 cephalic cases, and one with transverse presentation. There were eight sets of twins and in these the prolapse occurred six times in the first twin and twice in the second. There were 15 floating heads at the time of prolapse, while in 3 cases the head was in midpelvis and in 4 below the spines. Cervical dilatation was less than 5 cm. in three cases, 5 cm. or over in four, and complete in 15 cases. Eighteen cords prolapsed at the time of rupture of the membranes, twice at the time of expulsion of the bag in placenta previa. One occurred twelve hours after rupture of the membranes, and one twenty-four hours after rupture. In 16 cases the bag of waters ruptured spontaneously, in six there was artificial rupture. In 10 cases of the 22 the bag of waters ruptured before entrance to the hospital.

The management of these cases was as follows: In one a Voorhees' bag was inserted after replacement of the cord, which was followed by spontaneous delivery of a live baby. Low forceps yielded a live baby in one case. In 9 cases there was an extraction of the breech with one death. Version and extraction was performed in three cases with one death. A Braxton Hicks' version was carried out in one case of placenta previa with loss of that baby. Spontaneous delivery occurred in four. The cord was replaced, Trendelenburg position used and breech extraction employed in one case; version and extraction and Dührssen's incision on 8 cm. cervix were undertaken in 1. Finally in 1 case spontaneous delivery followed the replacement of the cord, the pushing of the head into the pelvis and the Trendelenburg position.

The circumstances associated with the prolapse were these: Spontaneous rupture of the bag of waters in breech in seven cases; forelying cord and spontaneous rupture of bag of waters in 3; floating head, early spontaneous rupture of bag of waters in 3; artificial rupture for delivery of breech in 2; artificial rupture, insertion of bag and prolapse with expulsion of bag in 2; artificial rupture of bag of waters for bleeding in 2; membranes ruptured twelve hours, not in labor, prolapse at time of complete dilatation in 1; transverse presentation with ruptured bag of waters in 1; prolapse when head pushed up for manual rotation in 1.

The attending staff at Cook County Hospital is practically unanimous in the opinion that an intact bag of waters is a most valuable aid in the successful termination of labor, and the general policy of the clinic is to preserve the bag of waters until the cervix is completely dilated. Prevention of prolapse of the cord is only one of the reasons for this practice. Artificial rupture is performed only for the induction of labor in the most urgent cases, as in threatened eclampsia, and for the intraovular introduction of a bag or the treatment of marginal placenta previa.

In 14 cases, in the series reported, premature artificial rupture of the bag of waters preceded the prolapse, and in five instances, the cord prolapsed immediately after the bag of waters was ruptured. The question naturally arises, what would have happened to these 14 cases if the bag of waters had not been prematurely ruptured? Does the advantage expected from the artificial rupture of the bag of waters fully justify the risk?

DR. C. C. DRAA.—At the Presbyterian Hospital in Chicago during the last six years we have delivered 5,035 mothers, with the occurrence of prolapse of the cord in 18, giving us an incidence of 0.35 per cent as compared with Dr. Mengert's figure of 0.66 per cent. The etiologic factors in our series appeared to be a large baby, in six instances, and a contracted pelvis, in one instance. There were bag inductions in 3 cases and transverse presentations in 2 instances. There were 5 cases of breech presentations, and 2 twin pregnancies. The length of the cord was stated in only 3 cases in each of which it was noted to be abnormally long.

The method of treatment in our series was usually immediate delivery, because as a rule the cervix was completely or almost completely dilated. Version and extraction was resorted to in 10 cases; simple extraction of a breech presentation in 5 instances, and normal delivery occurred in 2 cases after replacing the cord. There was one forceps delivery.

The fetal mortality was quite interesting, in that the gross uncorrected mortality was 38 per cent. If we eliminate the previable babies the gross mortality was 22 per cent, which compares favorably with Dr. Mengert's series in which the gross fetal mortality corrected was 46.6 per cent. The main difference in the two series as we have tried to study them is first, the percentage incidence of prolapse of the cord, and second, the infant mortality.

Rupture of the membranes for induction of labor appears to be an important etiologic factor in producing prolapse of the cord. In Dr. Mengert's report of 58 cases of prolapsed cord, the membranes were ruptured artificially 21 times and yet one gathers the impression that he does not consider it of major etiologic importance.

Further as to fetal mortality it is obvious that the cord cannot prolapse until the membranes are ruptured, and second, the fetal mortality is lower with the greater dilatation present at the time of prolapse. So it seems that maintaining

the integrity of the membranes until they rupture spontaneously or until the cervix is sufficiently dilated that the descent of the head can be controlled so as to prevent prolapse of the cord is the better plan. As we have shown, practically all of our patients were deliverable at the time the membranes ruptured either artificially or spontaneously.

DR. RUDOLPH W. HOLMES.—There are two types of cord prolapse: one, the forelying cord before the membranes are ruptured, and the other the technical prolapse after the membranes have ruptured. In the former an exaggerated Trendelenburg position may cause a recession of the head from the inlet, will obviate the risks of funic compression, and may permit the cord to float upwards into the uterine cavity for the specific gravity is slightly higher than that of the liquor amnii. In the meanwhile, preparations may be made for the introduction of the bag *outside of the membranes*, the one place where such procedure is permissible. When such artificial dilatation has progressed sufficiently for the introduction of the hand, the hand should repose the cord, rupturing the membranes if they have fortunately withstood the bag pressure, and the cord hung over the buttocks and leg that it may not prolapse again.

After there is a true funic prolapse, the Trendelenburg posture is equally necessary in order that pressure may be diminished while preparations are being made for some other recourse: First, manual reposition if the dilatation permits it; if not, then the replacement by the method Dr. Cary employs may be successful at times, though forty years ago this method was discarded by myself on account of the difficulties and failures. Where conditions permitted it, I have always felt version was the one most likely to bring success, but under any circumstance fetal mortality necessarily must be high. I have never felt that cesarean section was indicated for this condition, for the danger of infection from drawing the prolapsed cord through the uterine incision is to be remembered. If a section be done, before the fetal extraction, the cord must be clamped at the navel, and cut: when the infant is delivered the cord must again be cut at the placenta, and the cord then extracted through the vagina. Cesarean section should not be recommended for general practitioners or general surgeons, the mortality being what it is.

DR. MENGERT (closing).—Dr. Hillis has stressed the low incidence of prolapse of the cord on the service with which he is connected and has implied that artificial rupture of the membranes had something to do with our high incidence. If we take out the 14 cases of premature artificial rupture from the 58 cases of prolapse, 44 instances remain, which still represents twice as many as on Dr. Hillis' service.

One of the main purposes of this paper was to discuss the long cord and to stress that it is a factor over which we have no control in the etiology of prolapse. Whatever one believes with regard to the benefit of an intact bag of waters during labor, I do not believe that its rupture is by any means the whole story or even a major part in the etiology of prolapse of the funis.

Dr. Draa has emphasized the comparatively low mortality rates at the Presbyterian Hospital. In reply, I might point out that most of our deliveries are done by students and rotating interns. The interns rotate two months on our service and are supervised by an assistant resident who is in the early years of his training. I think it is understandable that in the excitement of the moment operations are done which might be avoided by men of mature experience.

EPIDEMIC INFECTIOUS DIARRHEA OF THE NEWBORN INFANT*

R. S. CRON, M.D., F.A.C.S., H. W. SHUTTER, M.D., AND
A. H. LAHMANN, M.D., F.A.C.S., MILWAUKEE, WIS.

EARLY in September of 1938 a tragedy in the form of an epidemic of infectious diarrhea occurred in the overcrowded nursery of the Milwaukee Hospital. The epidemic was severe and many infants died, with discouragingly few recoveries. It was not checked until the maternity floor was closed and renovated.

Epidemic diarrhea of the newborn is a unique disease entity. Its clinical picture is that of a severe intestinal intoxication. It is accompanied by watery yellow stools, abnormal distention, precipitous loss of weight, drowsiness, marked dehydration, toxicity, and shock.

EPIDEMIOLOGY

The prevalence of this epidemic form of diarrheal disease among newborn infants is reflected in New York's infant mortality statistics. Frant and Abramson² show that although a satisfactory reduction has been evidenced in death rates from all causes among infants from one month to one year of age, an analysis of the vital statistics of New York City proves that little has been accomplished in effecting a suitable lowering of the death rates among infants in the neonatal period. In fact, as far as diarrheal deaths are concerned, the rate shows a steady ascent in mortality among newborn babies during recent years. Frant and Abramson attribute this increased mortality to the previously unrecognized clinical entity, namely epidemic diarrhea of the newborn infant. They have followed twenty-three outbreaks similar to our own in fifteen hospitals giving maternity care. From July, 1934 to July, 1937, they have followed the postnatal course of 4,594 live born babies. Among these, 711 cases, or 15.5 per cent, developed the disease. Nearly one-half or 335 of those infected died. The average mortality rate for the 4,594 babies studied was 7.3 per cent. In our own epidemic 39 infants, 31 full term and 8 prematures, were either in or entered the nursery subsequently to the onset of this epidemic. At that time or subsequently thereafter 22, or 56 per cent, became ill and 18, or 82 per cent, of this group died.

The following facts in regard to the disease have been found. It occurs during the first two or three weeks of life and attacks both sexes of any race or nationality. Older children and adults coming in contact with the affected infants do not contract the disease. On the other hand infants with very little acquired immunity are most susceptible to it. There is no relationship between the disease and the state of nutrition of the infant, although immaturity and prematurity lower the infant's resistance. The disorder has been recognized only in cities of the United States and countries lying within the North Temperate Zone.

In our epidemic, the probable source of infection was traced to the father of one of the deceased babies who visited the mother during a nursing period. At that time he was convalescing from an acute coryza and diarrhea. The baby on its sixth neonatal day, which was forty-eight hours following the father's visit, appeared ill, was immediately isolated with special nursing care, and it died in

*Presented at a meeting of the Chicago Gynecological Society, February 16, 1940.

forty-eight hours. Because infectious diarrhea was suspected the entire obstetric floor was closed the same day and 23 apparently healthy babies discharged from the hospital while three infected ones were transferred to the pediatric department. Seven infants under isolation technique remained in the nursery.

During the following week 14 of the 23 infants who had been discharged were readmitted. All of these and the remaining 7 infants were isolated in private rooms with special nursing care and various pediatricians in attendance. The 7 mentioned above and 11 of the 14 readmitted infants contracted the disease and died.

According to the literature, no differences are evident in the frequency of the disease among either breast or artificially fed infants. This distinction is no longer so sharply defined because of the present practice of giving supplementary feedings to nearly all newborn infants. In our epidemic, 18 of 25 babies who were being fed on formulas, the day the obstetric floor was closed, died. All of these babies had been residents of the nursery for from three to twenty-eight days. The other 7 babies who did not contract the disease were in the case of two, inhabitants of the nursery for three days, one for two days, and the remaining 4 were born the day the nursery was closed. Six babies, ages seven to fourteen days, who received breast milk and one formula feeding, and 8 more, ages seven to eleven days, who obtained breast milk after having been on formulas for three or four days, either did not contract the disease, or if they did, survived their illness. Two babies who were discharged three or four days, respectively, before the ward was closed subsequently developed the disease. From the above facts it is evident that the formula-fed babies died while the breast-fed ones survived, although all babies received some formula.

Formula-Fed Babies

Died	18	Ages, 3-28 days
Lived	7	Ages, 1-3 days

Breast-Fed Babies

Died	None
Lived	6 Ages, 7-14 days

Formula- But Subsequently Breast-Fed Babies

Died	None
Lived	8 Ages, 5-11 days

PATHOLOGY

Autopsies were performed upon 16 of the 18 babies that died in Milwaukee Hospital. One-half, or 50 per cent, of these infants were premature. Marked dehydration and emaciation was the most conspicuous finding in 14, or 87 per cent. Acute enteritis was the most common lesion in 87 per cent, and pneumonia was next most frequently found, although it predominated over all other findings in only three of the babies examined. Often the pneumonia was the result of aspiration of food. In two of these, pneumonia was undoubtedly the cause of death for there was no evidence of enteritis.

PHYSIOLOGY

Diarrhea is a common disorder and is manifested in a great number of diseases, some of which are not primarily gastroenteric. Increased peristalsis and increased frequency of evacuation of the intestines occur in most febrile diseases, especially respiratory infections, in toxic or altered metabolic states, such as uremia and acidosis, exposure to high or low external temperatures, and in certain types of allergy. Diarrhea in early infancy is of special significance, because the younger the child the greater are the consequences of the loss of water and electrolytes.

Loss of weight is largely due to dehydration of the body. Water and salts are lost in large quantities from the interstitial spaces, and the plasma volume is reduced. The most important cause of the production of acidosis is undoubtedly severe loss of base in the stools. If there is inadequate renal function, sufficient acid is not secreted by the kidneys and compensation is not provided.

Clauson has shown that in conditions of dehydration lactic acid in the blood may be greatly increased.

In diarrhea much of the carbohydrate undergoes fermentation with the production of the lower volatile fatty acids. Acids with less than twenty carbon atoms can be recovered from the stools in increased amounts. These were formerly called irritants and thought of as an etiologic factor, but recently this has been shown to be doubtful. Altered chemical conditions, especially in the duodenum, which normally is sterile, permit abnormal amounts of bacterial growth. It is suggested by Plantenga and Jordan that these organisms elaborate toxic products. The absorption of foodstuffs is inadequate due to rapid peristalsis, and possibly, also, to an inability of the intestinal epithelium to absorb them.

Protein metabolism is very little affected, but fats and carbohydrates are considerably so. Much of the fat intake is found in the stool, mainly in the form of mineral fat. Carbohydrates are absorbed poorly, and the residuum is fermented, and the products of fermentation can be recovered from the stool.

Besides loss of water in the stools, a loss of minerals is also important, especially sodium, potassium, and chlorine. Acidosis results if elimination by other organs of the body is insufficient.

BACTERIOLOGY

Bacteriologic procedures have failed to discover a common etiologic agent. It seems apparent that the bacteriologic studies of infectious diarrhea in the newborn present a special problem. It is evident that infants are nonresistant to organisms which are of little or no virulence to the adult. It is probable that infection in the newborn infant often has its origin in adults with mild diarrhea. The hemolytic streptococcus was certainly the most common one isolated. From the stools it was cultured in all 16 cases studied. Blood cultures showed it twice, and, in throat cultures taken on 14 affected babies, it appeared in 100 per cent of the cases.

Post-mortem bacteriology also showed a prevalence of hemolytic streptococcal infections. Cultures of peritoneal fluid made on 13 babies showed this organism in 10 or 77 per cent, negative in 2 or 8 per cent and a mixed infection in the remaining one. Blood cultures revealed hemolytic streptococci in 2, or 14 per cent, gram-negative bacilli in 2, or 14 per cent, and pneumococci in 1, or 7 per cent. One lung culture showed hemolytic streptococci. Blood cultures were negative in 9, or 64 per cent.

SYMPTOMATOLOGY AND FINDINGS

At times the condition was preceded for one or two days by prodromal symptoms such as occasional vomiting, arrested weight gain, listlessness, and refusal at feedings. More often, however, the onset was acute and the clinical picture rapid in its course. A healthy robust baby within twenty-four hours would appear shocked and prostrated. The incubation period varied from forty-eight to ninety-six hours.

Diarrhea was usually the symptom presented in the beginning. The stools were increased in frequency to four and five daily. Consistency was good except that now and then a loose stool was passed. Soon, however, the frequency of the stools increased and finally they became only loose and watery. Usually, the stools were yellow, and occasionally greenish in color. The stools contained no curds or blood but occasionally mucus. Some of our babies were passing as many as seventeen stools a day.

Loss of weight was second in appearance. Even babies who had only a mild attack of diarrhea lost considerable weight due to dehydration. The mucous membranes were dry, there was loss of skin turgor, the eyes were sunken, the facies wrinkled, the fontanels sunken, the abdomen retracted, and the color cyanotic and then ashen gray, and a mental torpor with a feeble cry was present.

The temperature might be slightly elevated from 99° to 100° F. Occasionally, those with complications ran a fever as high as 103° or 104° F. Some of the babies even showed a subnormal temperature.

Distention was frequently present. Loss of appetite was a common symptom. Vomiting frequently occurred with regurgitation of food and subsequent aspiration of it into the bronchi, resulting in a pneumonia. A very few of the babies exhibited peristalsis.

TREATMENT

As far as treatment of the really sick baby was concerned, results were uniformly disappointing. In general, the infants did not respond satisfactorily to the recognized modes of therapy in diarrheal disorders. The usual measures of replenishing the dehydrated tissues, nourishing the patient, alkalization, restoration and maintenance of mineral balance, and putting the bowel to rest were utilized.

A few of the special measures which were tried were the administration of a solution of 0.8 Gm. of sulfanilamide in 100 c.c. of normal saline subcutaneously in doses of 25 c.c. twice daily or 1 gr. of prontosil or 1 c.c. of neoprontosil given orally. These were rather heroic measures, and it is doubtful if they were of benefit to the infants. Transfusions of blood from donors who had taken 60 gr. of sulfanilamide in the twenty-four hours just prior to the giving of blood were also used. Convalescent serum was another agent used, but its efficacy could not be determined because numerous other agents were also being administered at the same time. The same was true of diplococcic filtrate and autogenous vaccine.

In the Milwaukee epidemic, breast milk was found to be an important adjunct in the treatment of infantile diarrhea. Not until the epidemic was well advanced was it possible to obtain a sufficient supply of mother's breast milk for these infants. Upon appeal to the Chicago Commissioner of Health, Dr. Bundeson, an ample supply was shipped to Milwaukee daily. Babies nursed upon human milk from the time of their birth were the only ones who either escaped or survived the epidemic.

Control measures employed prior to the outbreak of the epidemic were the usual ones laid down for the care of the infant from birth to its entrance into the nursery and thereafter. The basic principle involved was that everything coming in contact with the baby's mouth or nose should be in a surgically aseptic condition.

In all probability the simplest solution of this problem is the dispersion of the nursery. Spivek suggests an increasing degree of dispersion and safety by using: (1) cubicle units each completely equipped; (2) nurseries of no more than three or four beds to be closely associated with a similar number of maternal beds; (3) newborn infants housed in rooms adjacent to or in the mother's room; (4) hospital delivery and discharge within forty-eight hours, and (5) the ultimate of dispersion, frank home delivery.

Since the epidemic of 1938, the nursery at Milwaukee Hospital is being maintained under very strict precautionary measures. Overcrowding has been avoided and the nursery has been broken up into three divisions. Two are located on the third floor and will be designated as nurseries "A" and "B," and a third is on the fourth floor which accommodates any overflow and will be called nursery "C." Both nurseries on the third floor have been equipped with air-conditioned cubicles. Nursery "A" accommodates 18 cubicles while nursery "B" which is completely air conditioned in itself contains 12 similar air-conditioned cubicles. There are no cubicles in the fourth floor nursery but there is available 4,446 cubic feet of space for 12 cribs. An isolation room is maintained in another section of the hospital for the care of infected or suspected babies.

The cubicles can best be described by studying the illustration (Fig. 1). It is noted that air is sucked in through a filter in the top, and that the baby is completely isolated by glass partitions and front window. All clothing is stored in cabinet below. The babies are fed their formula, bathed, and diapered by the nurse without being removed from the cubicle or crib. The danger of contamination from the dressing or diapering table is thereby avoided. Each baby is carried individually and not in a conveyer to its mother. Special nurses and of course visitors do not enter the nursery. Attending physicians and nurses wear

caps, masks and gowns in the nursery. Nurses having skin infections and colds are excluded from the nursery. Throat cultures should be done on all nurses before they begin nursery service. The importance of hand washing is stressed especially between babies, before feedings, and after changing diapers.

All formula is prepared, bottled, capped, and labeled in a laboratory adjacent to nurseries "A" and "B" by a graduate nurse who has no other duties. Of course all equipment and bottles are autoclaved.



Fig. 1.

Children are not permitted on the maternity floor. Visiting should be discouraged, and during nursing hours is forbidden. Sitting and laying of outer garments on beds by visitors is discouraged.

All infants' records are kept at a desk outside of the nurseries. With this arrangement and the necessity of the attending physician donning cap, mask, and gown before entering the nursery, traffic in and out is reduced to a minimum.

The efficiency with which air conditioning and isolation by means of cubicles has reduced the possibility of air-borne infections is amply illustrated by the results of exposing culture plates. Open Petri dishes containing media for the

growth of hemolytic and nonhemolytic streptococci were left for a fixed period of time in occupied and unoccupied cubicles and in all of the nurseries. They were then incubated and the colonies counted. The most striking finding was the comparatively high count found in nursery "A." There nursing activity is the greatest and the air unfiltered. Three to ten times as many organisms were present in comparison to findings in a smaller air-conditioned nursery "B" directly across the corridor. The cubicles, however, in both nurseries showed similar minimal bacterial growths, demonstrating that the filter of the cubicle can reduce the air-borne infections satisfactorily. It was found that unoccupied, recently cleaned cubicles and cubicles with recently changed filters had the lowest number of organisms. In nursery "C," where crib space is the maximum and activity the minimum, bacterial counts were no higher than those found in the cubicles. Nonhemolytic streptococci were found about ten times as often as were the hemolytic type.

SUMMARY

1. Epidemic infectious diarrhea is a definite entity.
2. The disease is extremely contagious. More than one-half of the infants exposed to the infection contracted the disease.
3. Acute enteritis and pneumonia were the most common pathologic findings.
4. Bacteriologic studies showed that the most common invading organism was the hemolytic streptococcus. The average incubation period for development of symptoms varied from forty-eight to ninety-six hours.
5. The severity of the infection was illustrated by the rapid progress of the disease and its concomitant very high mortality rate, namely, 82 per cent.
6. Only formula-fed babies died. Breast-fed infants either did not contract the disease or if they did were able to conquer the infection.
7. Treatment was unavailing except for the feeding of mother's milk.
8. The small nursery with air-conditioning unit permits the growth of the minimum number of air-borne bacteria. Air-conditioned cubicles in large nurseries accomplish the same thing but cubicles add the important factor of isolation to the protection of the baby. Many small air-conditioned units containing individual cubicles with a completely isolated formula kitchen are the ideal set-up for the modern hospital nursery.

CONCLUSIONS

Tremendous immunity and therapeusis are conferred to a nursing by the feeding of mother's milk. Since the epidemic, a strenuous effort has been made to increase the incidence of breast feeding.

Grateful acknowledgement is made to Dr. C. J. Allen for material used in this paper.

REFERENCES

- (1) *Frant, Samuel, and Abramson, Harold*: J. Pediat. 11: 772, 1937. (2) *Idem*: Am. J. Pub. Health 28: 36, 1938. (3) *Rice, John L., Best, William H., Frant, Samuel, and Abramson, Harold*: J. A. M. A. 109: 475, 1937. (4) *Holt, L. E., and McIntosh, R.*: Diseases of Infancy and Childhood, ed. 10, 1933, D. Appleton-Century Co., pp. 181-185. (5) *Clausen*: Am. J. Dis. Child. 29: 761, 1925. (6) *Spivek, Mandel L.*: J. A. M. A. 111: 1065, 1938.

THE EFFECT OF THYROID ON STERILITY IN NORMAL AND HYPOTHYROID FEMALES

L. B. WINKELSTEIN, M.S., M.D., NEW YORK, N. Y.

(From the Gynecological Department of the Stuyvesant Polyclinic and Hospital)

INTERRELATIONSHIP between the thyroid gland and gonadal function has long been suspected (Marine¹ and Achnour²), and a large amount of data correlating sterility with cretinism and myxedema, in both males and females, has been accumulated. Moreover, milder conditions of hypofunction of the thyroid gland are thought also to be a factor especially where no other demonstrable pathology exists. This latter fact was first suggested by Litzenberg³ who demonstrated that 45 per cent of those having a low basal metabolic rate were sterile. Likewise, Rowe⁴ also showed that abnormal thyroid function is associated with sterility in over 30 per cent of a series of 2,549 cases. Although Berkman⁵ and Hutchens⁶ warn that a low basal figure is not always indicative of thyroid dysfunction (but should be considered as an indication of some metabolic or endocrine disorder), many⁷ have recommended that thyroid extract be given routinely, even to those with a normal basal metabolism, feeling that this is a valuable adjuvant because of its stimulating properties.

The present investigation was undertaken, to determine the efficacy of giving desiccated thyroid to a group of sterile women, whether or not demonstrable thyroid hypofunction was present.

MATERIAL

All patients, with few exceptions, were from the service of an active gynecologic clinic. They represent a fair cross section of the reproductive span of the average female, the youngest being 21 years, the oldest 40 years of age. The average for the studied group of cases was 29.9 years at the time treatment was started.

In all, 71 cases with a normal or lowered basal metabolism were investigated, of which only 16 were selected for the present study. The latter were chosen because, as far as could be determined, they were entirely free from all pathologic processes, the correction of which might possibly have been effective in relieving the sterility. Thus, for example, one case, presenting clinical evidences of hypothyroidism, was excluded, because of a second degree retroversion and an endocervicitis.

It was felt, therefore, that the 16 selected cases might demonstrate the efficacy of thyroid therapy, since all other known factors which might be instrumental in producing sterility were eliminated.

No patient was considered as sterile until at least one full year had elapsed after marriage, during which time, notwithstanding normally frequent sex relations and the absence of contraceptive devices, pregnancy had not occurred.

METHODS

After taking a complete history, a thorough physical examination was made, at which time all endocrine stigmas were carefully noted. Laboratory analyses consisted of complete blood counts and chemistry; routine smears for the gonococcus, and hanging drops for the *Trichomonas vaginalis*; urinalysis; Wassermann; and determination of the basal metabolic rate. In those instances where repetition of the basal rate was deemed necessary, the lower, or lowest figure was considered as most correct.

Wherever possible, either a fresh or a condom specimen of the husband's seminal fluid was examined. Spermatozoa counts, number of abnormal forms, compatibility with the endocervical mucus of the wife (Kurzrock⁸) and duration of viability were recorded.

Since occlusion, spasm, or stricture of the Fallopian tubes is one of the largest single mechanical factors causing sterility, the presence of this pathology would have to be eliminated. Therefore, in most cases, tubal insufflation was performed according to the technique of Rubin.⁹

Desiccated thyroid (U.S.P.-X) was given each patient, starting with 1 gr. per day and increasing the dose 0.5 to 1 gr. per day at semiweekly intervals, until a maintenance tolerance was reached. Constant checks for changes in blood pressure and pulse rate, for the appearance of fine muscular tremors, and for the presence of urinary sugar and albumin, especially where a normal metabolism was present, were made at frequent intervals. The basal rate was often rechecked after thyroid had been given for four to five weeks, and by adjusting the dosage, the rate was kept between a +10 per cent and a +20 per cent; i.e., at or just above the upper normal limits. If weight loss was desired, a low caloric diet was given, but no patient was advised to lose more than 2 to 2.5 pounds per week.

Thyroid was continued indefinitely at optimal dosage, and as soon as pregnancy was definitely established, the amount was readjusted. This readjustment was a reduction in amount, as pregnancy progressed, from one-third to one-half the maximal prenatal dose, since Baer¹⁰ and Cornell¹¹ have shown that the basal rate increases from 25 to 35 per cent above the normal as term is approached. Medication also was continued during pregnancy, as prophylaxis against abortion,^{3, 12, 13} and because it was felt that the strain, even with a mild thyroid deficiency, might lead to toxemia.¹⁴⁻¹⁶

RESULTS

Since the 16 cases, selected from the entire series, were free of pathology, they may be taken as a criterion of the efficacy of thyroid therapy in relieving sterility. These cases, accordingly, were classified into two separate categories, 9 patients who successfully conceived (Group A) and 7 who remained sterile (Group B). A complete summary of the findings for these two groups is presented in Tables I and II.

Examination of these tables reveals certain facts, which require further elucidation:

Menses.—Menstrual disorders were common, but more so in Group A, where 77 per cent suffered from abnormalities of the flow itself. In 7 cases clots were noticed. Menorrhagia was present in 3 cases, dysmenorrhea in 4, and oligomenorrhea in 1. One patient (6-A) who had been sterile for fifteen years, and who was under treatment solely for obesity and mild menopausal complaints, stated that, although her cycle was perfectly normal, the amount of flow had decreased considerably during the twelve months preceding treatment. In Group B, 71 per cent had menstrual disturbances, 2 complaining of menorrhagia, 3 of dysmenorrhea, and 1 of oligomenorrhea.

Irregularity in the cycle itself was far more marked in the A group (55 per cent). Since periods varied from nineteen to forty-six days, no definite rhythm could be established in 4 cases (2-A, 3-A, 4-A, and 5-A). In Group B this particular abnormality was encountered less frequently (14 per cent), only one

TABLE I. GROUP A* (BECAME PREGNANT)

Case	1	2	3	4	5	6	7	8	9
Age (years)	28	27	26	29	29	40	21	32	29
Married	6 yr.	5 yr.	5 yr.	3 yr.	---	15 plus yr.	19 mo.	---	4½ yr.
Duration of sterility	5 yr.	6 yr.	18 plus mo.	2 plus yr.	14 mo.	15 yr.	19 mo.	6 yr.	1½ yr.
Catamenia	14/21-31/4 Dysmenor- rhagia	12/28-36/5 plus Menorrhagia	12/25-35/2½	14/19-46/2 Dysmenor- rhagia, oligomen- orrhagia	13/28-36/5 Dysmenor- rhagia, menor- rhagia	15/28/2-3 Menopause	13/28/4 Menor- rhagia	13/21-28/6 Menorrhagia	14/31/5 Dysmenor- rhagia
Premenstrual tension	++ backache	+ headache (1 day) backache	+++ backache (1 day)	++ nervous- ness backache headache (3-4 days)	0	0	++ (1 day)	++ headache (1-2 days)	+++ (2 days)
Libido	Mild	None	None	Mild	Normal	None	None	Mild	Mild
Weight (pounds)	178	212	144	152	138	176	130	186	140
Height (inches)	60	60	60	62	60	62	63	59	61
Insufflation	(1) normal	(1) normal	(1) normal	(1) mild spasticity	(1) normal	---	---	---	Normal

Endocrine stigmas	Dryness of skin, scalp and hair; hair on face; pelvic hair abnormal	Brittle nails; dryness of skin and scalp; thick coarse skin; hair on face; pelvic hair very thick; enlarged thyroid; pitting edema (subclinical myxedema)	Hair on face; dryness of skin and scalp; slight exophthalmos	None	None	Dryness of hair and skin; facial hair; pelvic hair abnormal	Mild pitting edema	Dryness of hair; abnormal pelvic hair of male type; facial hair; brittle nails	Dryness of skin, scalp and hair; facial hair; enlargement of thyroid
Basal metabolic rate	-10%; -12%	-28%; -28%	-26%	-10%	-16%; -18%	-14%	-10%	-18%	-12%
Cholesterol (mg./c.c.)	178	385	400	---	---	220	155	---	200
Thyroid (gr.)	iii	xii-xxiv†	iv	iii	iii	iv	iss	iv	iii
Duration sterility after thyroid (months)	12	13 (2)†	4	7	5	3	4	6	6
Pregnancy	Normal	Hypertensive toxemia	Normal—secondary intra-labor; postpartum hemorrhage	3 weeks premature	Normal	Induced abortion	Spontaneous abortion due to accident	Normal	Normal, premature 1 month

*In all cases blood counts, urinalyses, Wassermann reactions and semen analyses were normal.

†This patient took 12 gr. of thyroid per day for 11+ months; through error dosage was doubled (24 gr. per day) for 2+ months.

TABLE V. CAUSES OF DEATH

Uremia		30
Hemorrhage		13
Ante partum	5	
Post partum	5	
Cerebral	1	
Liver	1	
Skin (purpuric)	1	
Acute heart failure		3
Acute yellow atrophy		2
Single cause		40 cases
Combined causes		4 cases

There were also 4 cases of post-partum hemorrhage and 3 of the patients showed hemorrhage in unusual situations, including the brain, liver, and the skin in the form of purpura.

More emphasis should be placed on hemorrhage and shock when considering chronic nephritis.

The liver and heart are also damaged in this disease as shown by 2 cases of acute yellow atrophy, 1 of massive hemorrhage of the liver, and 3 cases of acute cardiac dilatation.

METHOD OF DELIVERY

In severe chronic nephritis termination of the pregnancy is the indicated treatment. In this series termination was advised twenty-seven times; in 5 cases the advice was refused and in one case spontaneous delivery occurred before induction could be started.

Eight patients were delivered by cesarean section (7 abdominal and 1 vaginal). Thirteen had induction of labor, of which 7 delivered spontaneously, 3 by version, 2 by forceps, and 1 by therapeutic abortion.

The need of relief in these recognized desperate cases accounts for the high incidence of cesarean section. Three cesarean sections were performed after conservative treatment failed; 1 was for premature separation of the placenta and 4 because of the severe toxemia which required prompt termination of the pregnancy.

TABLE VI. METHOD OF DELIVERY

Abortion		3
Normal		17
Version		3
Forceps		2
Cesarean section		7
Vaginal cesarean section		1
Undelivered		10
Induction		13
Puncture membranes	6	
Medical	3	
Pack	1	
Bag and pack	1	
Puncture and bougie	1	
Dilatation and evacuation	1	

Including cesarean section total number of pregnancies terminated is 21.

TABLE VII. BABIES

BORN ALIVE	STILLBORN	DIED	UNDELIVERED	UNKNOWN
14	11	5	10	4
Infant mortality rate 68 per cent.				

Hypertension was the one symptom common to all and is rightly accepted as the chief and earliest symptom. The majority (32 cases) had a systolic pressure between 140 and 200. Two had pressures as high as 300 and over and only two had a pressure between 130 and 140 when first observed. One of these died of adherent placenta, post-partum hemorrhage, and shock. The other showed a rising pressure which reached 204 at delivery when she developed eclampsia, coma, uremia, and died ten days post partum.

TABLE IV. FREQUENCY OF SYMPTOMS

Hypertension		44
Edema		36
Ascites and hydrothorax	1	
Pulmonary	1	
Cerebral	1	
Coma		34
Convulsions	22	
Albuminuria		33
Headache		28
Nitrogen retention		23
Nausea and vomiting		21
Obesity		20
Amaurosis		20
(Eye grounds examined in 8)		
Hemorrhage		13
<i>All but five showed convulsions and coma</i>		

Edema was the next most common symptom and usually generalized over the body. Pulmonary and cerebral forms were probably more common than actually noted, but hydrothorax and ascites were unique.

Coma and convulsions were almost as common as hypertension; in fact, there were only 5 deaths in which neither convulsions nor coma occurred. These exceptions were due to:

1. Post-partum hemorrhage and shock following cesarean section.
2. Cesarean section followed by anuria and fever.
3. Retained placenta with death under anesthesia.
4. Cerebral hemorrhage, post partum, in a mild nephritic with a blood pressure of 150/100.
5. Acute cardiac dilatation five days post partum.

Albuminuria, although not common to all, was one of the most significant signs. It developed early, even before hypertension in three cases, and was a persistent danger sign.

Headache, gastric symptoms, and nitrogen retention were all observed as late symptoms and need no comment.

Obesity was present to a remarkable degree and far out of proportion to the usual occurrence. Four patients weighed more than 200 pounds. Twenty were noted as obese, 7 as average, 4 as thin. In 13 there was no record of weight or comment as to size. This high incidence of obesity would suggest a serious disturbance of metabolism and the endocrine system as an underlying cause of chronic vascular and kidney disease.

Eye grounds were rarely studied; the ophthalmoscope was used only eight times although amaurosis was recorded in 20 cases. This is an error on the part of the attending physician. The presence of retinitis or hemorrhage will show at once the seriousness of the case.

Uremia was the cause of death in the great majority, but hemorrhage was a common complication (13 cases). This is primarily due to the effect of nephritis on the placenta causing abortion (3 cases), miscarriage (1 case), premature placental separation (3 cases), and placenta previa (1 case, probably frank bleeding of premature separation).

2. If this fails or the case is severe the pregnancy should be terminated to save the mother's life.

In order to evaluate the severity of the disease, the following studies should be made: (1) Blood pressure; (2) weight; (3) physical examination for edema and cardiac damage; (4) fluid intake and output; (5) urinalysis; (6) renal function tests: (a) Fishberg concentration and (b) fractional phenolsulphonephthalein test as described by Stander; (7) eye ground examination; and (8) blood total nonprotein nitrogen for nitrogen retention.

These are simple standard examinations that can be done by any physician, with the exception of the single blood chemistry estimate, and will give information of ample degree of accuracy to indicate termination of pregnancy. They should be repeated as often as necessary to reach accurate conclusions.

The following may be listed as serious danger signs and positive indications for immediate interruption:

1. Rapidly rising blood pressure or a systolic pressure of 180 or above.
2. Amaurosis with retinitis or retinal hemorrhage.
3. Persistent albuminuria, increasing in quantity.
4. Nitrogen retention, nonprotein nitrogen above 45 mg. per 100 c.c.
5. Increasing edema or marked edema that does not respond to treatment.
6. Signs of cerebral irritation as persistent headache, gastric symptoms, epigastric pain.

If coma and convulsions develop, then delay has been too long and the patient should be treated as an eclamptic. Careful study will bring about an early recognition of the serious sign before the disease reaches a desperate condition.

In selecting the method for interrupting the pregnancy, two facts should be kept in mind: (1) the danger of hemorrhage, and (2) nephritics are more likely to develop shock than ordinary normal pregnant women.

The following methods are suggested:

First Trimester.—Abdominal hysterectomy where patient's condition warrants the risk, otherwise therapeutic abortion with later sterilization.

Second Trimester.—Puncture of membranes and bougie with later sterilization or abdominal hysterectomy if physical condition warrants the risk; although the bougie has a greater risk of infection, it is a surer method of induction.

Third Trimester.—Puncture of membranes and medical induction using not more than 20 gr. (1.3 Gm.) of quinine or pitocin in only 0.1 c.c. doses.

If rapid evacuation is imperative, classic cesarean section.

After coma and convulsions develop, the patient should be treated as an eclamptic. Conservative measures should be used, no surgery attempted, until she is out of her convulsive state, then the pregnancy terminated.

SUMMARY

The analysis of 44 fatal cases of chronic nephritis complicated by pregnancy shows that two-thirds of the primary mortality is preventable, of which two-thirds are due to lack of prenatal care and ignorance of the patient and one-third due to errors of judgment on the part of

AVOIDABLE FACTORS

Fifteen of the cases were considered nonpreventable tragedies by the committee because the disease was too far advanced to save the patient.

Twenty-nine, or 66 per cent, were thought to be avoidable. Nineteen (43 per cent) were due to the ignorance or indifference of the patient, usually because she did not report for prenatal care or did not follow her medical advice as to proper bed rest, hospitalization, etc.

TABLE VIII. PREVENTABILITY

Unavoidable		15
Preventable		29
Patient		19
Lack of prenatal care and ignorance	14	
Refusal to follow advice	5	
Physicians' errors		10
Delay in proper treatment	7	
Inadequate prenatal care	1	
Neglect of a home case	1	
Error in surgical judgment	1	
66 per cent avoidable, 43 per cent due to patient, 23 per cent due to physician.		

Ten deaths (23 per cent) were considered due to an error of judgment on the part of the physician, chiefly because he refused to recognize the seriousness of the case. An example of this was the case of a para i whose condition was recognized at the thirtieth week of pregnancy, and she was hospitalized for three periods of nineteen, eleven, and eleven days, at the end of which time labor was induced. It was too late; she died of uremia eight days after the birth of the stillborn child. Two deaths were due to medical neglect and one to an error of surgical judgment in a case of premature separation of the placenta with hemorrhage.

COMMENT

These facts show the necessity for review of the obstetric care offered our patients. Even in a serious disease like chronic nephritis most of the deaths are unnecessary and about one-fourth are due to errors of the attending physician. Therefore, the following schedule of study and treatment is offered as a minimum standard that will provide thoroughly adequate care. The object is to make it so practical that it can be used in a small hospital with minimum laboratory facilities as successfully as in a large institution with every resource. All but one of the studies can be done by a capable physician in the patient's home.

When the patient first reports for obstetric care, the history should elicit evidence of previous kidney or arterial disease, including repeated abortions. Usually the patient will volunteer the information before she is asked. She should also be observed for obesity; and if it is present to any great degree, she should be classed as a potential nephritic.

Once the diagnosis of chronic nephritis is made it should be remembered that the essential pathologic lesions are vasospasm of the arteries and progressive kidney damage with secondary effects on the other organs as the liver, heart, and brain.

There are only two methods available in the management of this disease:

1. Rest, salt-poor and low-protein diet, and maintenance of fluid balance prevent edema and carry the pregnancy as far along as possible to obtain a viable child.

arteriosclerosis, the relationship was just the reverse, for it was a vasospastic disorder which caused thickening and stiffening of the blood vessels, and hence, was responsible for the arteriosclerosis. Just when we felt that we had emancipated ourselves from the idea that the kidney was responsible for hypertension, however, Goldblatt, by his very ingenious experiments on dogs, led us right back to the renal origin of hypertension.

Views on the nature of kidney disease and the toxemia of pregnancy have run a similar circular course. Originally, it was held that toxemia was nephritic in origin and then gradually we came to the opposite conclusion, that the toxemia of pregnancy was not of renal origin but instead that it arose from some unknown toxic source and resulted in damage to the kidneys. Largely through the efforts of Herrick and Tillman we learned that not only did the toxemia of pregnancy injure the kidneys but that more often it resulted in irreparable damage to the vascular system so that perhaps in one-half of all cases of toxemia of pregnancy, hypertensive-vascular disease would certainly follow within a period of a few years. Yet now Peters of Yale is once more insisting upon the importance of a renal lesion in the background of toxemia of pregnancy. He is particularly concerned with pyelitis and pyelonephritis as predisposing factors, but there is as yet no widespread clinical confirmation of his views.

In regard to Dr. Paxson's suggestions about treatment I would raise one question in regard to limitation of protein. The restriction of proteins in patients with all forms of kidney disease is a hang-over from the days when we thought that protein was injurious to the kidneys. We have changed our ideas considerably in this regard and Strauss has even suggested in his recent study that instead of withholding protein from the patient who shows evidences of toxemia, proteins are necessary in large amounts. The same thing is true in kidney disease with a loss of a large amount of protein in the urine and a consequent depletion of the blood protein. Here proteins must be given in larger instead of smaller quantities than normal.

DR. OWEN J. TOLAND.—The third table showed that 40 women died of chronic nephritis but only 9 were primiparas. The presumption might be that in their previous pregnancies, most of the 29 multiparous patients showed some evidence of hypertensive disease. The easier place to have handled this problem would have been at the end of such previous pregnancies. I think it is merely a question of a few more years until abdominal sterilization will be offered routinely for such patients.

DR. JAMES LEWIS.—I would like to ask what constitutes an unavoidable case. If the patient had adequate prenatal care and there was no delay in instituting treatment, where was the unavoidable factor?

DR. PAXSON (closing).—First, what is the unavoidable case? A woman with a systolic blood pressure of 150 delivered spontaneously and eight days later dies of cerebral hemorrhage, ought to be considered unavoidable. Unless you terminate all pregnancies with a blood pressure over 130, I think you must consider that case as unavoidable. Then you will always have that group of women who prefer to stick by their religious convictions. We class that as unavoidable, believing that a human being has the right to follow her religious belief on the subject. A case of premature separation of the placenta is another example; a woman with a moderately elevated blood pressure and slight evidence of chronic nephritis develops placental abruption, is rushed to the hospital, and section is done, but she dies. I think that is unavoidable.

I agree with Dr. Toland. Twenty-five of these women gave histories of one type or another suggestive of kidney and arterial damage. On the other hand, the others did not, and possibly a history of previous kidney damage would have been obtained could we have interviewed the patients before they died, but we only had hospital data to go by, and some of the records were not as complete as they might have been.

the physicians. The chief error in medical care was failure to recognize the seriousness of the situation and failure to terminate pregnancy promptly.

In addition to the usual symptoms of the disease, the frequency of obesity and hemorrhage is demonstrated as serious complicating factors. The failure to study eye grounds is noted with the recommendation that an ophthalmoscope should be part of the standard equipment of a maternity and that the eye grounds should be studied by the obstetricians.

A minimum standard is offered for the diagnostic study and evaluation of the disease with definite indications for termination of pregnancy.

I wish to express my thanks to Dr. Williams for assistance and guidance and to Mrs. William Reishtein and Miss Malkiel whose help in obtaining data and preparing statistics was invaluable.

REFERENCES

Stander, H. J.: Textbook of Obstetrics (Williams), ed. 7, New York, 1936, D. Appleton-Century Co. *Stander, H. J.*: Toxemias of Pregnancy, Wm. Wood. & Co., N. Y., 1929. *Smith, Weiss, Lilly, Konzelman, and Gault*: Cardiovascular Renal Disease, Springfield, Ill., 1939, Charles C. Thomas' Co.

DISCUSSION

DR. PHILIP F. WILLIAMS.—The diagnosis of nephritis in pregnancy is a difficult one, so that it is possible that some of the cases that Dr. Paxson reported may not have been this disease. Likewise, I would not be surprised if some cases of chronic nephritis which came before the Committee have been missed for several reasons. In the first place some toxemias simulate an acute toxemia overlying a chronic nephritis. In the second place due to the lack of the history and other findings just referred to, patients with chronic nephritis have probably been put down as true toxemia without knowledge of the previous renal lesions. It is difficult to establish the diagnosis of chronic nephritis in the toxemic woman who first is seen after six and one-half months.

There is a far broader implication in this paper, however, namely, the prevention of pregnancy in women with a constitutional impairment of this type. With further education of the public regarding periodic health examinations more and more women will seek premarital and preconceptional examinations. When this happy day arrives, we may be able to determine certain cases in which the occurrence of pregnancy would be detrimental, and to these could be suggested the use of contraceptive measures. Not all patients with chronic nephritis will need to have pregnancy prevented but the knowledge of its pre-existence when pregnancy supervenes will enable us to supervise a pregnancy to a far better degree.

DR. EDWARD WEISS.—The subject of kidney disease and pregnancy has been a confused one for several reasons: first, because of the old belief that the toxemia of pregnancy was of "nephritic" origin and that the convulsive seizures were "uremic"; second, because of the failure to differentiate glomerulonephritis, pyelonephritis, and essential hypertension complicated by pregnancy; third, because of the attempt to remedy this situation by the invention of such terms as sub-standard or low reserve kidney; fourth, because of the lack of accurate knowledge as to the remote effects of the toxemia of pregnancy on the cardiovascular-renal system of the mother.

When we first became aware of the importance of high blood pressure from a clinical standpoint, it was thought that arteriosclerosis was responsible and that the patient was doomed to die of kidney disease. About the turn of the present century, largely due to the efforts of Allbutt in England, Huchard in France and Janeway in America, we learned that most hypertension was of nonrenal origin, that is, it was of the so-called "essential" variety. Instead of being caused by

eighteenth. By 11:00 A.M., the pressure was unchanged, but there was some blurring of vision again and photophobia. She had passed 20 ounces of urine since 9:00 A.M., having a 3-plus albumin and a specific gravity of 1.011. At 2:30 P.M. her blood pressure was 138/88 and uterine contractions began. By 6:00 P.M. her pressure had climbed to 170/116, she had passed but two ounces of urine in the last three hours and there was a 2-plus albumin in this. She was slightly drowsy henceforth, and in hard labor. At 8:30 P.M. she was delivered of a 4-pound 11½ ounce healthy male child. Just prior to delivery her pressure had reached 170/112. Ten minutes after the birth it was 124/76, but there was no evidence of shock. The placenta was small and showed 10 large round white infarcts penetrating its whole thickness. The progynon B was repeated and ¼ gr. of morphia was given. She had an easy night. Next day she voided freely, had a slight edema of the fingers and toes, no complaints of any kind, and was bright and cheery. Her pressure hovered about 120/80 on several readings. A catheter urine showed 3-plus albumin still. The edema had increased by nightfall; accordingly 10,000 I.U. progynon B were given. The edema had disappeared by morning. She had an uneventful recovery and is still perfectly well with a blood pressure of 126/70.

CASE 2.—(Courtesy of Dr. J. F. Simpson.) In her first pregnancy Mrs. P., aged 30 years, had had blindness in one eye for two weeks following delivery. In the ensuing seven years she had five spontaneous abortions and miscarriages at one to six months of gestation. In 1937 a pregnancy characterized by severe "pre-eclampsia" occurred. An induction was done and a living child was secured. Pulmonary embolism followed, associated with phlebitis of the left leg.

Her last menstrual period began on June 2, 1938. The pregnancy proceeded uneventfully in the early months. However, she complained of dizziness and visual specks on Sept. 23, 1938, when she had a blood pressure of 140/80, but no albuminuria. Her physician gave her epsom salts every second day as well as a salt-free diet, and she carried on normally until a transient left-sided hemiparesis developed on Jan. 2, 1939, associated with a clear urine and a blood pressure of 120/70. On January 25 the pressure was 140/90. On February 8 the pressure had climbed to 160/98, the edema was considerable, and there was a 2-plus albumin in the urine for the first time. On February 17 her pressure was 180/105, her urine showed 4-plus albumin, there was much edema and visual disturbances were marked. Next day her blood estrin was negative and she was put to bed and given 10,000 I.U. of progynon B intramuscularly. Her pressure was 185/105. On February 19 the progynon B was repeated at the same dosage, a good diuresis occurred in the night, and her pressure fell to 175/100. Her visual symptoms promptly cleared. On February 20 another 10,000 I.U. of progynon B were given and the pressure soon fell to 175/94. On February 21 she went into labor spontaneously and in five hours delivered a 5-pound baby boy. On March 3 her pressure was 134/70. After her uneventful recovery an x-ray sterilization was done. On March 17, 1939, her blood pressure was 142/82, and the mother and child have been well since.

CASE 3.—In her first pregnancy, Mrs. B., aged 33 years, had had toxemia with repeated hemorrhages. Her last period began July 25, 1939. She was first seen Feb. 28, 1939, when seven months pregnant. She had put on 47 pounds of weight in this pregnancy up to that time, attaining a weight of 193, had a blood pressure of 118/70, and had edema of the legs extending nearly to the hip. She was taken off of salt and milk. Her blood estrin was negative. By March 7 she had developed frequent occipital headaches, had gained to 195 pounds, had a pressure of 130/76, and had a 2-plus albumin in the urine. She was then given 50,000 I.U. of progynon B and three tablets per day of progynon-DH. On March 11 there was only a trace of albumin in the urine, much less leg edema; her weight was 194 and her pressure 138/76. The headaches were unchanged. The dose of 50,000 I.U. of progynon B was repeated. On the sixteenth she received 20,000 I.U. of progynon B. On the twenty-first her weight was 197, her pressure 122/74, urine clear, the headaches had gone, and she volunteered she felt "marvelous." On the twenty-eighth there was enormous edema of both legs and one of them was "numb to the hip." Her weight was only 196, however, and her pressure 128/80. There was

THE EFFECT OF ESTROGENS ON TRUE PRE-ECLAMPSIA AND ECLAMPSIA

EVAN SHUTE, B.A., M.B., F.R.C.S.C., LONDON, ONTARIO, CANADA
INCLUDING A BRIEF NOTE BY M. M. O. BARRIE, B.Sc., LONDON, ENGLAND

IT IS generally recognized that physiologic pregnancy is largely under hormonal control. It should not be surprising, therefore, if many of the features of pathologic pregnancy are evidences of hormonal dysfunction or uncontrol. For example, in 1935 the Smiths¹ reported that the blood of eclamptic patients revealed low values for estrin. My studies supported this conclusion and I began to treat eclampsia with this in mind. As improvement appeared to follow such therapy,² I have continued it and present several protocols here in the effort to stimulate further interest in the method. It should be noted that the original finding of the Smiths has since been confirmed by Muhlbock³ and that Siegler⁴ also has reported a good result after the use of estrogens in pre-eclampsia.

In my first paper on this therapeutic method, I gave the protocols of one pre-eclamptic and 2 eclamptic women treated with estrogens. Here-with are the records of 7 more pre-eclampsies and of 2 convulsive eclamptic patients. All other true pre-eclamptic patients have reacted well to this treatment, but the cases presented are illustrative of what may be expected.

CASE 1.—Mrs. F., aged 27 years, had had a normal pregnancy three years before, followed by phlebitis. She was first seen Jan. 21, 1937 with a recurrent phlebitis in one leg, the first suggestion of another pregnancy. Her last period had begun on Dec. 25, 1936. There was vaginal bleeding on January 23, with pelvic pain and severe sacral backache. This was promptly controlled with wheat germ oil. The phlebitis soon subsided. Her weight at that time was 117 and her blood pressure 114/66. Her urine was clear. She stopped taking the wheat germ oil soon after her first threatened abortion, but was forced to return to it temporarily on May 21, as uterine tenderness had returned. On July 16 her weight was 136 and blood pressure 108/68. She had had no wheat germ oil since the end of May. On August 3 her weight was 146, her pressure 132/76, and there was considerable edema of the face, fingers, and left leg, as well as much visual disturbance. She was promptly taken off salt and milk. By the seventh her weight had fallen one pound, her pressure was 118/80, the edema had decreased, but a few uterine cramps had appeared. She felt well until September 11, when her weight had increased to 153, her pressure was 126/86, there was less edema, but the urine showed a 2-plus albumin in a two-basin sample. On the twelfth she developed a persistent parietal headache which lasted for three days, her pressure soon rose to 162/100, and she had epigastric distress, blurred vision, and backache, but no uterine contractions and no edema. She was given $\frac{1}{4}$ gr. of morphia and 10,000 I.U. of progynon B at 8:00 A.M. on the sixteenth of September. By the next day her headache had disappeared but she was somewhat dizzy. Her eyesight improved rapidly. She passed a mere 3 ounces of urine during the night before 7:00 A.M., but passed as much more in the next two hours. Her blood pressure at 8:00 A.M. was still 152/98 and her urine showed a 3-plus albumin. The progynon B was repeated in the same dosage and medical induction was begun, with artificial rupture of the membranes at 9:00 A.M. on the

ful." The dosage of stilbestrol was doubled. On the twenty-third her weight had fallen to 145 and blood pressure to 144/86. There was no edema. On April 2 the pressure had jumped to 170/102, weight to 146, there was slight leg edema and a 2-plus albuminuria. Stilbestrol per day was increased to 3 mg. On the sixth her weight was 142, urine clear, pressure 164/94. She was given 50,000 I.U. of progynon B. On the ninth day her weight was 142, pressure 156/88, the albumin 2-plus, and the hypodermic of 50,000 I.U. of progynon B was repeated. There were never any headaches nor visual disturbances now or later. On the thirteenth she revealed a weight of 141, albumin one-plus, and a pressure of 156/84. She had received 20,000 I.U. of progynon B on the eleventh and this was now repeated. On the sixteenth her weight was 141, there was slight leg edema, and the pressure was 174/102. The head had been deeply fixed since March 23, and the urine showed a 2-plus albumin. The 20,000 I.U. of progynon B were repeated. On the seventeenth she had an induction with castor oil and artificial rupture of the membranes (after breaking down a conglutination of the cervical canal). Her vaginal and cervical tissues were soft and I thought she could deliver vaginally. She had hard uterine contractions all afternoon without effecting any dilatation of the cervix. Accordingly a low cesarean section was done twelve hours after the rupture of the membranes. The placenta appeared grossly normal. The uterine wall at operation bled less than at any cesarean section I have ever seen, curiously enough! The postoperative course was completely afebrile and uneventful. The male child weighed 7 pounds 4 ounces and did well. Her blood pressure on May 30, 1940, was 150/88 and she has remained well, with no exacerbation of her pernicious anemia.

CASE 6.—(Courtesy Dr. H. Mosser.) Mrs. F., aged 29 years. Her last menses had begun on Aug. 15, 1939. There was a history of short cycles with rather heavy flows at the periods. There was some nausea and vomiting in the early months of pregnancy. On Oct. 24, 1939, her weight was 134 and blood pressure 114/70. On October 30, the blood estrin was negative and urine normal. On January 12 her weight was 152 and blood pressure 126/80. The urine was negative. By February 7 her weight had increased to 159 but the urine was still normal. There was some edema of the extremities on arising each morning, however. There was the suggestion of some hydramnios. Her physician gave her wheat germ oil on the strength of the hydramnios and despite the negative blood estrin found earlier. She promptly gained 8 pounds in the next twenty days on this regime, and on February 27 her blood pressure had risen to 130/90. A blood estrin repeated on March 2 was again negative and, perhaps because no oil had been taken since February 27, her pressure had reverted to 114/70 and the urine was normal. She was put on 3 mg. of stilbestrol each day, and on March 16 her weight was 170 and pressure 126/90. The urine was normal. There was only slight ankle edema. The dose of stilbestrol was raised to 4 mg. per day and she at once reported an increased output of urine. On March 30 her weight was 170, the blood pressure was 124/84 and there was a faint trace of albumin in the urine. On April 3 the edema and albuminuria were the same, the weight was 173, and the pressure was 120/80. On May 4 there had been a transient headache, her weight was 181 pounds, and pressure 134/94. There was still a faint trace of albumin in the urine. On May 7 she spontaneously had "show," with a blood pressure of 150/100, and she was sent to the hospital at 11:30 A.M. She was promptly given 50,000 I.U. of progynon B. This was repeated at 4:00 P.M. and the membranes were ruptured artificially. Labor began promptly and terminated at 11:00 P.M. in the delivery of a normal 8-pound 8-ounce male. The next day her pressure was 130/90 and she voided normally. On May 15 her pressure was 112/70. On June 22 the pressure was 120/78.

CASE 7.—(Courtesy of Dr. H. Pink.) Mrs. H., aged 39 years, had had two children. Her last menstrual date was Dec. 1, 1938. She was first seen by me on July 30, 1939, in the hospital, at which time her blood pressure was 150/88 and there was no edema, but she had had persistent headaches and visual disturbances, with a one-plus albumin in the urine. She was then 7½ months pregnant. She had a negative blood estrin, and therefore was discharged on 1 mg. of stilbestrol each day. On August 18 she was again admitted with a story of severe headaches for the previous two days, oliguria for two days, but no visual disturbance and no

a smaller urine output and a 2-plus albumin. She was given 50,000 I.U. of progynon B. On April 1 her weight was 200, her pressure 130/74, both legs had improved, but the headache had returned. Her measured urinary output for the preceding four days had been about 1,000 c.c. per day. She had passed only 400 c.c. in the twelve hours prior to her visit to the office, although she had been drinking a large amount of fluid. The urine was clear of albumin, however. She was given 50,000 I.U. of progynon intramuscularly and put on 1100 I.U. theelol per day. This was soon changed to 1 mg. of stilbestrol per day. On April 6 her weight was 196 and blood pressure 118/72. The headache had gone, but there was a 3-plus albumin in the voided urine. Twice a week for the next month she received 50,000 I.U. of progynon B in addition to her daily stilbestrol. On April 27 her blood pressure was 110/68, weight 200, and urinary output had risen to 1,600 c.c. per diem. On May 4 her pressure was 156/80, weight 200 pounds, and the urine showed a plus albumin. On May 5 a medical induction was done, followed by artificial rupture of the membranes. Two hours after labor began, she delivered a 9-pound 14-ounce normal male. One tiny white infarct was seen on the edge of the placenta on its maternal aspect. The patient had an easy convalescence. On June 17, 1939, her weight was 175 and her blood pressure 124/84.

CASE 4.—(Courtesy Dr. H. Mosser.) Mrs. T., aged 29 years, had spent three years in a sanatorium for tuberculosis during her adolescence and was still on pneumothorax therapy. She had had two boys, the younger being 6 years old. These had been normal pregnancies in each case. The menstrual history was normal. Her last menstrual period was on May 2, 1939. On Oct. 1, 1939, her weight was 132, representing a gain of 10 pounds in the pregnancy up to that time, her blood pressure was 124/82 and the urine was negative. On November 2, there was some edema of the legs and headache was severe and constant. The weight was now 142 pounds, of which 4 pounds had been gained in the previous week. The blood pressure was 126/90, and there was a trace of albumin in the urine. An estrin test done on the blood was negative. Therefore on November 3 she was given 20,000 I.U. of progynon B intramuscularly. Her blood pressure by that time had risen to 130/96. On November 4 she reported less edema and an increased urinary output during the night. The blood pressure had fallen to 126/80. The dose of progynon B was repeated and she was put on 2 mg. of stilbestrol daily. On November 9, the weight was 140, the blood pressure 124/90, and there was a trace of albumin in the urine. On November 26, the weight was the same, the pressure 124/80, the urine showed a one-plus albumin, and the stilbestrol was therefore raised to 3 mg. per day. On January 1 there was no change. On January 18 the weight was 144, the pressure 130/90, and the edema was increased. On February 4 there was no albumin, the weight was 143, and the pressure 138/90. On February 9 at 5:00 P.M. spontaneous labor began, the blood pressure being 166/110 and the patient somewhat dull mentally. A catheter urine showed a 2-plus albumin, no casts, and 3 to 5 pus cells per high power field. She was given 50,000 I.U. of progynon B at this time. The pressure was 138/70 at 9:00 P.M. The membranes were ruptured artificially in order to expedite labor, and normal delivery occurred an hour later of a male child weighing 8 pounds 1 ounce. The post-partum course was uneventful. The pressure on the day after delivery was 140/80 and on July 20 was 126/80.

CASE 5.—Mrs. D., aged 45 years, had had no previous pregnancies here. Her last menstrual period began on July 7, 1939. She was first seen on Oct. 3, 1939, when two or more months pregnant. She had been under treatment for pernicious anemia with cord changes for the preceding fourteen months. Her weight was 130 and blood pressure 140/84 when first seen. The blood estrin was negative. By January 4 her weight had risen to 140 and blood pressure to 138/88. The urine was clear of albumin. On March 7 there was a sudden weight gain of 7 pounds to 145, and the pressure jumped to 160/94. There was a slight edema and a trace of albumin in the urine. Her blood estrin was still negative. She was put on 1 mg. of stilbestrol per day. On the fourteenth her weight was 146, pressure 148/92, the edema was unchanged, the urine clear, and she "felt wonder-

TABLE II. GROUP B* (REMAINED STERILE)

Case	1	2	3	4	5	6	7
Age (years)	29	36	24	29	38	37	24
Married (years)	7	6 plus	2½	4	16	16	2½
Duration sterility	5 yr.	6 yr.	20 mo.	3 yr.	7 yr.	15 plus yr.	2 plus yr.
Catamenia	16/29-33/4 Dysmenorrhagia	14/28/5	11/28/4-6 Dysmenor- rhagia	12/31-39/2 Mild oligomen- orrhagia	13½/21/5	15/24-29/5 Dysmenorrhagia	13/28-30/5-6 Menorrhagia
Premenstrual ten- sion	++ (1 day)	+ (1 day)	++++ (4 days)	0	+ (1 day)	+++ (2 days)	+ (mild)
Libido	Subnormal	None	Normal	SL subnormal	None	Slight	None
Weight (pounds)	141	140	118	130	158	166	144
Height (inches)	64	62½	62	62	61½	63	62½
Insufflation	(2) Normal	(1) Normal	(1) Normal	(1) Normal	(1) Normal slight opacity	Normal	Normal
Endocrine stigmas	Hair on face; pel- vic hair showed male type	Dryness of skin, scalp; brittle nails; enlarged thyroid	None	None	Dryness of hair; facial hair marked	Hair on face; acne; enlarged thyroid	None
Basal metabolic rate	+14%; +7%	+8%; +12%	+10%; +12%	+11%; +3%	+10%; +10%	+4%; +8%	+9%; +11%
Cholesterol (mg./c.c.)	200	175	---	175	---	175	---
Thyroid (gr.)	ii-iii	i-iii	iv-v	ii-iii	iii-iv	iii	i-iii
Duration treatment (years)	2½	1½	1	1½	1 plus	2	1 plus

*In all cases, blood counts, urinalyses, Wassermann reactions and semen analyses were normal.

edema. She had a 2-plus albuminuria and was apparently due in two weeks. She was given 50,000 I.U. of progynon B intramuscularly, as well as a sedative. Spontaneous labor with hard pains began at 4:00 A.M. on August 19. Her blood pressure then was 166/86. A 2-plus albumin (catheter samples) persisted all that day, although she received 50,000 I.U. of progynon B at 10:30 A.M. and 1:00 P.M. At 5:00 P.M. her pressure was 140/70 and her urine output was scanty with no casts, but there were a few red blood cells in it. Labor began to slow up and the head was still unengaged. At 7:00 P.M. her blood pressure jumped suddenly to 170/110 and 50,000 I.U. of progynon were repeated. Her membranes were ruptured artificially and the cervix was dilated manually from a diameter of 3 up to 5 cm. dilatation under cyclopropane. Strong pains began at once and she delivered in bed in half an hour. A normal child of $5\frac{1}{2}$ pounds was born. The placenta was normal. A small post-partum hemorrhage kept up for the next three hours, at the end of which time her blood pressure had fallen to 134/38. The bleeding was then checked with ergometrine. On August 20, her blood pressure was 164/0. She had an uneventful recovery, revealing a large fibroid uterus as the puerperium passed. On August 22 her blood pressure was 154/76. Stilbestrol was continued. On the twenty-fifth her pressure was 128/78, the stilbestrol was stopped, and a moderate lactation ensued on the cessation of stilbestrol therapy. In June, 1940, her blood pressure was 120/70 and urine clear.

These protocols have been presented in great detail, with emphasis on the clinical aspects of the case histories. These were all private patients and the series is therefore uncontrolled. Most of the women were given too small doses of estrogens. Those with any experience of these cases will understand at a glance whether the therapy here described has been helpful. It should be remembered that none of these women was restricted in diet beyond decreasing salt intake in Cases 2 and 3, and there was absolutely no restriction of their usual activity in any patient but Case 2. Had bed rest been enforced generally the apparent benefits of the treatment upon blood pressures, for example, would undoubtedly have been more striking. It has seemed to me that the recovery of these women treated by estrogens has been very satisfactory. In many of them the blood pressure has reverted to normal within the first ten days post partum. That estrin can be given too late is illustrated by our fatal case (see below).

It may be objected, that the criteria I have used for the recognition of pre-eclampsia are open to criticism.^{5, 6} Certainly I do not regard as "pre-eclamptic" the great majority of toxic women usually so labeled,⁷ and would not expect the administration of estrogens to be helpful to all such women taken indiscriminately;⁸ therefore the protocols of two classical convulsive cases are here given.

CASE 1.—(Courtesy Dr. H. Mosser.) Mrs. H., aged 19 years, primipara, menstruated last on Nov. 27, 1938. Her weight on Feb. 1, 1939, was 100 pounds, blood pressure was 124/70, and the urine was clear of albumin. On July 31 the blood pressure was 150/100, a plus albuminuria had appeared and her weight was 118. On salt restriction the albumin cleared and the pressure fell to 126/100. She felt well. On August 13, she went swimming in the lake. Next morning she suddenly developed headache and epigastric distress, as well as an oliguria which she herself noticed. Her doctor at once rushed her into the hospital where a 3-plus albuminuria was found, as well as 5 pus cells per high power field. On that day at 2:00 P.M., when I saw her first, she had headache, no visual disturbances, some liver tenderness, and was vomiting. She was mentally clear. There was no edema. There were painless uterine contractions, the head was engaging, and her blood pressure was

206/158. A blood estrin was negative. 250,000 I.U. of progynon B were promptly given at 2:30 P.M. due to an interne's mistake! (50,000 I.U. had been the dose ordered.) At that time there was the first convulsion. Seven more convulsions occurred before 10:00 P.M. Finally they became almost continuous. After 2:30 P.M. there was an increasing stupor. The urine became increasingly bloody with hyaline and granular casts, and amounted to only 30 c.c. every three hours; 50,000 I.U. of progynon B were given at 9:00 P.M. Anuria developed at 1:00 A.M. in spite of 500 c.c. of 10 per cent glucose solution given by vein at midnight. The pressure had been 146/110 most of the afternoon, but this fell to 118/78 about 1:00 A.M. The fetal heart was normal until it ceased suddenly at 2:30 A.M. when her poor pains had effected 7 cm. dilatation. She died at 3:10 A.M. The autopsy (Dr. John Fisher) revealed necrosis and many hemorrhages in the enlarged liver, nephrosis, slight ascites and pleural effusion, pulmonary edema, an extensive fresh hemorrhage throughout the pons which had broken into the fourth ventricle, subendocardial and pulmonary hemorrhages, submucous bladder hemorrhages, and a purulent bronchitis. The undelivered female fetus weighed 2,200 Gm. and appeared normal. The placenta appeared normal. Microscopic study showed peripheral necrosis of the liver lobules about the portal areas. The hemorrhages extended beyond these areas. Elsewhere the liver cells were comparatively unchanged. The tubular epithelium of the kidneys was much swollen, nearly obliterating their lumina in certain areas. Many casts of all types were seen. The glomeruli were compact and ischemic. No vascular sclerosis nor hemorrhages were seen. The corpus luteum definitely was degenerating. In the pituitary the chromophil cells were unusually prominent and some of the eosinophilic cells were small and poorly defined. No definite necroses nor degeneration could be found there however.

CASE 2.—(Courtesy Dr. J. F. Simpson.) Mrs. A., aged 25 years, primipara. Her last menses began Oct. 3, 1938. I first saw her on July 5, 1939, at which time her blood pressure was 140/88, her urine solid with albumin, and she had become quite deaf. Her blood estrin was positive. A medical induction was advised and failed. On July 12 she was admitted to the hospital with the same degree of albuminuria, a marked oliguria, and a blood pressure of 140/108. She was dull and apathetic. Her blood estrin had become negative. There was no headache. Her edema markedly increased during the day. At noon her membranes were artificially ruptured. She soon went into labor, had one convulsion just after midnight and the child's scalp showed at 1:00 A.M. 50,000 I.U. of progynon B were promptly given. Manual rotation and forceps delivery of a persistent occipitoposterior were performed under ether anesthesia. A normal female child weighing 6 pounds 15 ounces was delivered, and a retention catheter was inserted. The placenta was quite normal in appearance. A moderate post-partum hemorrhage occurred. She became conscious at 3:30 A.M. and the progynon B was repeated at 5:00 A.M. but she was still slightly drowsy at 7:30 A.M. There was no urine output until 11:00 A.M. At 1:00 P.M. there was a 3-plus albumin. Up to 3:00 P.M. she had excreted 5 ounces and the progynon B was then repeated. At 5:00 P.M. there was only a trace of albumin in the urine!! In the first twenty-four hours after her delivery she voided 34 ounces of urine and also wet her bed, although her intake was but 24 ounces. On the thirteenth her pressure was 136/100, urine was clear, and the edema was rapidly disappearing, but a severe occipital headache lasted for the first three days of the puerperium. Her last progynon B was given on that day. By July 17 she appeared well but had a pressure of 138/96. She has been well since, but I have no later blood pressure or urine reports.

It will appear from the foregoing that the estrogens have an important place in the management of true pre-eclampsia and eclampsia. They are especially useful in maintaining urine output, decreasing albuminuria, and relieving the stupor, headache, and visual disturbances preceding and accompanying convulsions.

BARRIE'S OBSERVATIONS*

If low blood estrogen values play a vital role in the onset of eclampsia an antiestrogen such as vitamin E⁹ if given by mistake to a pre-eclamptic could be expected to depress these values still further and precipitate convulsions. One of my colleagues and I have had experiences suggesting that such was possible, as Case 6 might indicate, for example. Barrie¹⁰ has recently obtained some interesting data on animals to support such an opinion. I am permitted to quote her letter, now a year old, giving her preliminary observations in extenso:

"In 1939 (J. Obst. & Gynaec. Brit. Emp. 46: 49, 1939) an account was given of a number of cases of toxemia occurring in rats fed on a diet partially deficient in vitamin E. The pathologic changes included fatty infiltration of the liver, deposition of calcium salts in the kidneys, which also showed large amounts of albumin, and associated degeneration of the tubule cells. A number of cases have been observed in which the animals developed convulsions shortly before death. The following examples illustrate the conditions:

"Rat A was 4 months old and had been fed on a vitamin E-free diet from weaning. It was mated and given one very large dose of 2.5 mg. of d-l-a tocopherol (vitamin E) on the same day. On the eighteenth day of pregnancy the animal was extremely ill and there was blood on the fur around the mouth; on the following day it was having fits of violent convulsions; the head was drawn over to one side and then the rat turned over and over and stiffened its legs in a violent spasm which relaxed leaving the animal limp but with the head still drawn to one side. The rat was killed on the following day and 9 living fetuses were found in utero.

"Rat B was of the same age and had received the same diet and the same treatment. The convulsions occurred at intervals for 6 days preceding the birth of a live litter of 7. The head rocked backwards and forwards and the eyes rolled; the tail stiffened, then the body was drawn stiffly into a ball and thrown into the air several times with the violence of the convulsions.

"These observations can only be regarded as preliminary; there were about 20 such cases. No figure can yet be given for the frequency of occurrence among toxic rats and no adequate data relating the condition with dosage of vitamin E. Both the rats described were sterile before treatment and both received sufficient vitamin E on mating to produce a viable litter. I offer no explanation of the condition, but record it in view of the possibility that it may be in some way analogous to eclampsia in man."

DISCUSSION

I am aware that Young, Obata, and Oden¹¹ have produced convulsive deaths in laboratory animals by injections of placental extracts, Young and Obata claiming that the animals at autopsy showed eclamptic lesions. Oden was unable to confirm this histologic observation, however. Dieckmann¹² has reproduced in dogs the hepatic lesion described for eclampsia by means of intravenous injections of tissue fibrinogen, but his animals did not have convulsions. It appears that Barrie is the first one to reproduce in an animal both the convulsive signs of eclampsia and similar histologic characters by means of a dietary factor administered orally.

In my two cases already published, the women were undelivered when first seen, but labor supervened rather easily several hours after the exhibition of the estrogen. There was no evidence of a change in the estrogens in the blood for at least seven hours after estrin had been

*To be published in detail in a later paper.

given intramuscularly, but thereafter there were no convulsions, the stupor rapidly diminished, there was no important change in blood pressure, and the urinary albumin disappeared rapidly—in the post-partum case this was complete in eleven hours after being maximally heavy at delivery! There was continued excretion of urine and never complete oliguria. The dosage to be advised was uncertain from that experience, however.

Further use of this treatment has convinced me that it needs to be supplemented in the convulsing cases, but only in them, with sedatives such as morphia during at least the first seven hours after estrin has been given. But thereafter, if large enough doses of the latter have been used, the convulsive tendency ceases, stupor disappears gradually, the kidneys do not close down and may actually, as in one of our severe pre-eclamptics, show a decreasing albuminuria and excretion of less blood and casts even while the blood pressure is rising slightly. Labor can be induced readily by rupture of the membranes, at least in women in the last month of pregnancy, the pains are unusually effective, and may continue even when the woman is becoming moribund from intracranial hemorrhage, as in our fatal case. The course of these patients is unlike that of eclamptic patients treated with sedatives but without estrin, and in order to demonstrate this beyond cavil, our second convulsive case in this report received nothing but estrin. Obviously, the greatest flaw in the work is that it is a small and uncontrolled series. However, control was impossible as these were all either private patients or patients seen in consultation. The use of controls in such work raises a delicate ethical problem.

It is of interest that the fatal convulsive case did not show any change in her blood estrogen although the interne gave her 250,000 I.U. of progynon B by mistake!

A report in the literature¹³ suggesting that the use of an estrogen actually may precipitate eclamptic convulsions ignores the fact that the convulsions mentioned there came on long after the estrogen had been given (over twenty-one hours). My experience leads me to suspect that more estrin, rather than less, was demanded by the patient's condition.

SUMMARY

1. As an addition to the records of the pre-eclamptic and two eclamptic women treated by estrogens previously reported by me, the protocols of 7 more pre-eclamptic and 2 convulsive eclamptic patients similarly treated are given here.

2. These women were not restricted as regards activity or diet except for limitation of sodium chloride in several of them.

3. Barrie, working in England, has recorded eclamptic-like convulsions in certain E-defective rats suddenly given large doses of d-l-alpha-tocopherol. The histologic lesions in these animals simulated those of human eclampsia. I relate this to the theory that estrogen defect is an important factor in the onset of eclampsia, as vitamin E is antiestrogenic in character.

4. The clinical effects of estrogens on these women are slow in developing, but favorable influences on convulsions, stupor, blood pressure, urinary volume, and albumin have been observed.

I desire to thank Schering (Canada) Limited for the progynon B used in these studies.

REFERENCES

- (1) *Smith, G. F. S., and Smith, O. W.*: Surg. Gynec. Obst. 61: 175, 1935. (2) *Shute, E. F.*: Endocrinology 21: 594, 1937. (3) *Muhlbock, O.*: Lancet 1: 634, 1939. (4) *Siegler, S. L.*: J. Lab. & Clin. Med. 24: 1277, 1939. (5) *Shute, E. F.*: Surg. Gynec. Obst. 65: 480, 1937. (6) *Idem.*: AM. J. OBST. & GYNEC. 33: 429, 1937. (7) *Idem.*: Vitamin E Symposium, Soc. Chem. Industry, London, England, April, 1939. (8) *Smith, G. F. S., and Smith O. W.*: AM. J. OBST. & GYNEC. 36: 769, 1938. (9) *Shute, E. F.*: J. Obst. & Gynaec. Brit. Emp. 43: 74, 1936. (10) *Barrie, M. M. O.*: Personal communication. (11) *Oden, C. L. A.*: J. Mich. M. Soc. 24: 110, 1925. (12) *Dieckmann, W. J.*: AM. J. OBST. & GYNEC. 17: 454, 1929. (13) *Robinson, A. L., Datnow, M. M., and Jeffcoate, T. N. A.*: Brit. M. J. 1: 749, 1935.

THE RESULTS IN TREATMENT OF 600 INCOMPLETE ABORTIONS

HARRY P. MENCKEN, M.D., AND HENRY H. LANSMAN, M.D.,
FLUSHING, N. Y.

(From the Department of Obstetrics and Gynecology, Queens General Hospital)

APPROXIMATELY 150 patients, or 17 per cent, of the total admissions to the Gynecological Service of the Queens General Hospital, are admitted each year with the diagnosis of incomplete abortion, infected or otherwise. This is exclusive of those patients more than four and one-half months' gravid who are placed under the supervision of the Obstetrical Service.

A survey of the case records of 600 abortions on the Gynecological Service, from 1935 to 1940, is presented in this paper. Although therapy for the greater number was conservative, some patients were treated radically with less favorable results. In determining the proper therapy, the necessity of understanding thoroughly the pathology of this disease and its relationship to the bacteriologic findings cannot be overemphasized.

On admission to the hospital, the patient is tentatively classified in one of the following four groups:

I. *Incomplete Abortion, Afebrile.*—The temperature must be below 100.4°F., and there must be no history of induction or of chills or fever.

II. *Potentially Infected Abortion.*—The patient is afebrile on admission, but has a history of chills or fever, or of criminal interference.

III. *Infected Abortion.*—The temperature is at least 100.4°F., and there is no clinical evidence of extrauterine infection.

IV. *Septic Abortion.*—The patient is considered septic if signs point to an extension of the infection beyond the uterus, or if the blood culture is positive.

RESULTS IN GROUP I ABORTIONS

There were 423 patients who were afebrile on admission and gave no history of interference. Of these, 221 were curetted after being observed for forty-eight hours or more in the hospital. In the remainder of patients, the abortion was either completed spontaneously or by the removal of tissue lying free in the cervical canal. There were no deaths in the entire group.

Our results demonstrated that, although 40 per cent of our patients did not require curettage, their average hospital stay was seven days as compared to the five-day average for those patients who were curetted.

Hemorrhage rarely requires immediate curettage since, in almost all instances of severe bleeding, the cause is placental tissue in the cervical canal. Severe bleeding can be controlled by its removal merely with the ovum forceps.

We cannot overemphasize the necessity for waiting forty-eight hours before curetting any incomplete abortion for the following reasons:

1. Further information is often obtained from patients who, on admission, denied manipulation.

2. A normal temperature on admission may be the bottom of a spiking temperature that may become apparent the following day.

3. The vaginal examination on admission does not always reveal the presence of an extrauterine infection. An illustrative case is that of a patient who, on vaginal examination at the time of her entrance to the hospital, revealed no signs of extrauterine infection although the patient admitted recent criminal interference. On the next day, signs of a fulminating peritonitis were present. She died on the third day. We may assume that the infection had already spread beyond the uterine cavity when the patient was first examined, although time was necessary for this to be clinically evident.

RESULTS IN GROUP II ABORTIONS

There were 31 patients who were afebrile on admission, of whom 24 entered with a history of some form of mechanical interference with their pregnancy, and only 7 with chills or fever prior to entering the hospital. Twenty-nine of these patients remained afebrile, whereas 2 had a mild febrile course. Sixteen were curetted after five days of normal temperature with no resultant morbidity. There were no mortalities.

We have selected an arbitrary period of five days before curettage in this group because longer observation is warranted in a potentially infected case. Whatever minor infection that may have been present would have subsided, and sufficient immune bodies formed to prevent spread of any persistent infection following manipulation.

RESULTS IN GROUP III ABORTIONS

There were 117 cases on admission where the infection was limited to the uterus. All patients received supportive therapy, and one-fourth were given sulfanilamide in addition. Forty-five patients were curetted. Twenty-nine were curetted after being afebrile for more than five days, with a postoperative morbidity of 3.4 per cent. Of the remaining 16,

3 were curetted while mildly febrile, and 13 were curetted after an afebrile period of less than five days, with a gross morbidity of 50 per cent. There was 1 death in the entire group.

It is in the treatment of cases in Group III where the infection is presumably limited to the uterus that there is a major difference of opinion between schools of gynecology. Studdiford,¹ representing one group, favors immediate curettage of all Group III cases when the offending organism is not the *Streptococcus hemolyticus*. We share the opinion of the other school which employs conservative therapy because of the following:

1. The uterine culture taken on admission does not always reveal the true invading organism. We have observed on several occasions that a nonpathogenic or negative culture was obtained on admission, whereas pure cultures of *Streptococcus hemolyticus* were later isolated. This phenomenon may be explained by the invasion of the uterine wall by a minimal group of virulent hemolytic streptococci with insufficient numbers in the uterine cavity to give a positive culture.

2. As mentioned above, one cannot exclude by vaginal examination the presence of extrauterine infection.

3. We have had no deaths with conservative treatment of Group III cases. In our single death in this group, Case 40311, the patient was afebrile on admission and denied interference with her pregnancy. On the second day the temperature was 102°F. On vaginal examination there was no evidence of any extrauterine infection. Necrotic tissue was removed from the uterus with a sponge forceps. The temperature rose to 104°F. on the third and fourth days, and the patient died on the fifth day. Post-mortem examination revealed the presence of a diffuse peritonitis, acute suppurative endometritis and myometritis, thrombophlebitis of the broad ligament, and multiple abscesses of the lung. Blood and uterine cultures taken at autopsy were reported as *Streptococcus hemolyticus*. Sulfanilamide was not available. Apparently the patient had an extremely virulent type of infection which might not have responded to any form of therapy. It is conjectural as to what the effect of sulfanilamide might have been. The radical treatment of this case by the early invasion of the uterus with the ovum forceps might have been responsible for the rapid dissemination of the organism.

SULFANILAMIDE THERAPY

We have found sulfanilamide to be invaluable in the treatment of febrile abortions. Although we have only given the drug to 25 per cent of our Group III and 65 per cent of Group IV patients, it is our belief that all febrile abortions warrant sulfanilamide on admission. Our reasons are:

1. The identification of the organism from the uterine culture cannot be obtained in less than twelve to twenty-four hours. This would delay the early administration of the drug.

2. As before mentioned, the initial uterine culture may not indicate the true invading organism.

3. As soon as toxic manifestations appear, the drug can be withdrawn without serious damage to the patient.

Our mode of administration of sulfanilamide has been in the form of prontosil, neoprontosil, or prontosil. The dosage for prontosil was $\frac{3}{4}$ gr., for prontosil 1.5 c.c., and for neoprontosil 1 c.c., per pound of body weight in 4 divided doses for the first twenty-four hours. Whenever

possible, prontosil was the drug of choice, and this was administered with equal doses of sodium bicarbonate. Subsequent dosage depended upon the clinical course and the offending organism.

A. *Streptococcus Hemolyticus* Infections.—The total dose is repeated for the second day, three-fourths the dose for two days, and one-half the total dose thereafter. This amount is gradually reduced with clinical improvement of the patient.

B. *Infections Other Than Streptococcus Hemolyticus*.—A similar dosage is given. However, if the fever persists by the end of the first week, the uterine cultures should be repeated, and if hemolytic streptococci are not isolated at this time, the use of the drug is discontinued.

After the blood volume has been restored by transfusion and infusions, the total twenty-four-hour fluid intake is limited to 2,000 c.c. Complete blood counts are done before the drug is administered, and for the first three days, the fifth, and the seventh day, and twice weekly thereafter. The urine is examined daily for bile, albumin, and red blood cells. Blood chemistry determinations for nonprotein nitrogen, chloride, and carbon dioxide combining power are obtained when there is any question of renal impairment or acidosis. Blood titers for sulfanilamide were not determined routinely.

It is known² that not all strains of the *Streptococcus hemolyticus* are equally susceptible to the action of sulfanilamide, and that the infection is mild when the organism is not of the invasive strain. Furthermore, it was frequently noted that the high fever in Group III patients who had not received sulfanilamide would subside following spontaneous evacuation of placental tissue. If sulfanilamide had been given to these patients and one were hasty in his conclusions, further cures for the drug would have been recorded. Therefore, to determine its therapeutic value, results only for Group IV patients were considered.

RESULTS IN GROUP IV ABORTIONS

There were 29 patients who, on admission to the hospital, showed signs of extension of infection beyond the uterus. Of these, 20 survived and 9 died. Seventeen patients received sulfanilamide. Only 2 patients were curetted after a long afebrile period, and 3 required surgical drainage of pelvic abscesses with recovery.

In an analysis of the fatalities in this group, we would like to first summarize those cases which were probably hopeless on admission to the hospital.

The patient in Case 27408 entered the hospital with a history of previous manipulation, and a temperature of 100.4°F. In twenty-four hours there were clinical signs of a fulminating peritonitis, and the patient died on the third day. The post-mortem findings were: generalized peritonitis and septic embolic abscesses in the kidney and myocardium. Post-mortem cultures were reported as *Staphylococcus aureus hemolyticus*.

The patient in Case 16109 entered the hospital with a temperature of 104.4° F. *B. welchii* were isolated from the uterus and blood stream and, although the patient received specific antitoxin, she died on the fifth day. On post-mortem examination, a perforated uterus and peritonitis were found.

The patient in Case 56550 died after a febrile course of seventeen days. The post-mortem findings were: perforated uterus and generalized peritonitis. The cultures taken at autopsy were reported positive for *Staphylococcus aureus hemolyticus*. Sulfanilamide was administered.

Of the remaining 6 fatalities, the following 3 patients were treated at a time when sulfanilamide was not available. Two of these died of *Streptococcus hemolyticus* infections.

The patient in Case 10691 confessed to the insertion of a catheter several days before entering the hospital. The temperature was elevated for four days and then normal until she was discharged from the hospital on the thirteenth day. She was re-admitted eight days later after the re-insertion of a catheter. The temperature was normal on her second admission, and continued so for two days. A tender ovary was palpated. Cultures were not taken. A curettage was performed on the third day while the patient was afebrile. Following the procedure, the temperature rose to 102.6°F. The course of her disease was septic for twenty-four days when she died. Hemolytic streptococci were isolated from the blood stream during her illness. Post-mortem findings were: thrombophlebitis of the broad ligament, acute mitral and aortic endocarditis, and miliary abscesses of the myocardium. Even the more radical investigators do not favor curettage in the presence of extrauterine spread of an infection. In this case, the operator ignored the finding of a tender ovary and curetted the uterus.

The patient in Case 57204 entered the hospital with a temperature of 100.4°F. She denied interference with her pregnancy. Placental tissue present in the cervical canal was removed with the sponge forceps. On the second day, clinical signs of peritonitis were present and she died on the third day. On post-mortem examination, generalized peritonitis, septic endometritis, and an ovarian abscess were found. *Streptococcus hemolyticus* was isolated from the uterus. No cultures were taken before death.

Case 9745 denied interference with her pregnancy. The temperature on admission was 104° F. *Streptococcus hemolyticus* was isolated from the blood stream. The course of the disease was septic for seventeen days when she died. The post-mortem findings were: septic endometritis and thrombophlebitis, septic endocarditis, brain abscess and panophthalmia. The cultures taken at autopsy were reported as *Streptococcus hemolyticus*.

The following 3 fatal cases received sulfanilamide therapy.

The patient in Case 88486 was admitted with a temperature of 104.4°F. *Streptococcus hemolyticus* was isolated from the uterus and blood stream. On the second day, physical signs of acute bacterial endocarditis were present. After forty-eight hours of sulfanilamide therapy, the drug was discontinued because of a marked leucopenia. The patient died four days later. Post-mortem findings were: endometritis and acute bacterial endocarditis.

The patient in Case 84718 had a septic abortion induced by a "slippery elm." The temperature on admission was 103.4° F. Nonhemolytic streptococci were isolated from the uterus, whereas repeated blood cultures were sterile. The patient had a bilateral parametritis. On the fifth day the temperature rose to 106° F., and the course of her disease was septic for thirty-four days when she died. The post-mortem findings were: acute endometritis, thrombophlebitis of the broad ligament, septic pulmonary infarct, and generalized peritonitis. Hemolytic streptococci, however, were isolated from the post-mortem cultures. The patient received neoprontosil on the fifth day, and the routine dosage was continued for five days. At this time, jaundice and a leucopenia appeared, and the drug was discontinued. The white blood count returned to normal in two days, whereas the jaundice persisted for sixteen days. The patient died on the thirty-fourth day after admission. This case demonstrates that the initial uterine culture may not reveal the true invading organism.

The patient in Case 97236 had a septic abortion induced by a catheter. Her temperature was 104°F. on admission. The abortion was complicated by a parametritis. *B. coli* were isolated from the uterus and blood stream. Sulfanilamide was administered. The course of her disease was septic for twenty-five days when she died. The post-mortem findings were: septic endometritis, left tubo-ovarian abscess, left parametritis, left pelvic cellulitis, left pelvic abscess, recto-sigmoid abscess, and generalized peritonitis. Cultures taken at autopsy were reported as *B. coli*.

Of 21 patients in Group IV who received sulfanilamide therapy, 4 died. However, in reviewing these mortalities, described in detail above, we find that only 2 patients had *Streptococcus hemolyticus* infections. One, who showed clinical evidence of an acute bacterial endocarditis on the second day and died on the fifth day, was probably too far advanced for an adequate test of sulfanilamide. Unfortunately, the second patient developed a leucopenia and jaundice, forcing us to discontinue the drug after only five days of treatment.

On the other hand, we have had 3 patients with pelvic peritonitis due to the *Streptococcus hemolyticus* who recovered under sulfanilamide therapy. Hitherto, these cases were considered hopeless.

The patient in Case 91199 was admitted with the diagnosis of parametritis and pelvic peritonitis. Hemolytic streptococci were isolated from the uterus and blood stream. Ochsner regime was instituted and, in addition, she received neoprontosil and repeated small blood transfusions. The temperature subsided by lysis at the end of the ninth day of hospitalization.

The patients in Cases 99367 and 85650 had positive uterine cultures for *Streptococcus hemolyticus*, whereas the blood cultures were sterile. Routine treatment was administered. The former was febrile for eight days, and the latter for six days.

Case 78992 entered the hospital with a parametritis and positive blood and uterine *Streptococcus hemolyticus* cultures. Under prontosil therapy, she became afebrile in five days.

Two patients were admitted with parametritis and had positive *Streptococcus hemolyticus* cultures only of the uterus. Under prontosil therapy, 1 was febrile for thirty-five days and the other for six days.

There were 7 patients with parametritis, of whom 4 were due to the *Streptococcus hemolyticus*, 1 to the *Streptococcus nonhemolyticus* and *B. coli*, 1 to a *Streptococcus viridans* and *B. coli*, and 1 to a *Streptococcus viridans*. None of these had a positive blood culture. All received sulfanilamide; however, their average morbidity was nineteen days as compared to eleven days in the above similarly treated *Streptococcus hemolyticus* group.

There were no deaths attributed to sulfanilamide, although we had to discontinue the drug in 7 patients (out of 17) in Group IV because of toxic manifestations. These included 2 patients with jaundice and leucopenia, 2 with leucopenia, 1 with leucopenia and a persistence of fever, and another with a persistent diarrhea. The frequency of toxic symptoms in this group can be attributed to the relatively large dosage of the drug given.

DISCUSSION

We have had good results with the conservative treatment of abortions where the infection is apparently limited to the uterus. The only patient of this group who died received radical therapy.

case presenting any marked deviation. These findings agree essentially with those of Lawrence and Rowe,¹⁷ who have demonstrated that menstrual disturbances, independent of pelvic disease, were common in this type of patient.

Premenstrual tension, in different degrees of intensity and duration, occurred frequently. The symptoms causing the greatest number of complaints, in order of severity and frequency, were: Lower back pain, nervousness, irritability and headache, starting from one to four days before the onset, during the period itself, or in one instance, postmenstrually. This was most marked in Case 3-B, where excitability, depression, and exhausting nervousness, three to four days premenstrually, necessitated confinement to bed for that period.

As the result of the administration of thyroid, the intermenstrual intervals tended to approach an average, especially in those cases where a lowered basal metabolism was found. However, no change in the character of the menses themselves occurred, except for a mild relief of dysmenorrhea in 2 cases (4-A, 4-B). Premenstrual tension was increased in 7 cases, relieved in 5, and unchanged in the remaining 4. No correlating factor could be found to explain these results.

Libido.—Although the number of sexual congresses was considered normal, the degree of libido was low. In Group A, 44 per cent were completely frigid; 44 per cent had a mild degree of sexual satisfaction, and only 12 per cent were normal. In Group B, 28 per cent were frigid, 52 per cent subnormal, and the remainder normal. Slight increases were noted after the administration of thyroid, in both groups, but not sufficient to find agreement with Murray,¹⁸ who believes that the effect of thyroid in sterility is due, in part, to increased libido occurring after its administration.

Obesity.—Obesity, per se, may act as a mechanical deterrent to fertilization, due, either to improper copulation or improper dissemination of the ejaculate in the vaginal vault. In comparing with the average height-age-weight tables, a marked tendency toward obesity is noted, Group A being 34 per cent overweight (average weight 163 pounds, statistical average 121 pounds) and Group B, 12 per cent overweight (average weight 142 pounds, statistical average 126 pounds).

Weight loss with thyroid, and where necessary a low caloric diet, was gradual. The maximum in any one week was 8 pounds (2-A) and the average from 2 to 2½ pounds. Weight loss was proportionally greater in those women who were markedly obese, despite the fact that all were taking tolerance doses of thyroid. With only one exception (2-A) the average weight at which conception occurred in Group A was 132 pounds. In those cases which remained sterile (Group B) the minimal weight during the period of study was also 132 pounds. It is interesting to note that the one exception (2-A) was 173 pounds when she conceived. These findings would militate against the factor of obesity as a deterrent to conception.

Endocrine Status.—Endocrine stigmas, other than obesity and menstrual disturbances, were far more common in the A than in the B Group. In the A Group, abnormal dryness of the skin, scalp, and hair were present in 5 cases; abnormal hair distribution on the face, cheeks, upper lip, and chin in 7 cases; extreme brittleness of the nails in 7 cases; and enlargement of the thyroid in 2 cases.

In the B Group, abnormal dryness of the skin and appendages, and abnormal hair distribution occurred in 3 cases and enlargement of the thyroid in 2 cases.

Subjectively, over 75 per cent of Group A patients complained of variable degrees of lethargy, inability to concentrate, undue weariness and fatigue, weakness and inability to withstand the cold. While these complaints were also present in the second group, they existed in a much milder degree.

With the administration of thyroid, rapid and marked relief of all subjective symptoms occurred. This was especially noted in those cases where several subclinical signs of hypothyroidism were present. However, in these latter cases, changes in the skin, hair texture, and nails occurred more gradually. Hair distribution remained unaffected.

Basal Metabolic Rate, Cholesterol and Thyroid Status.—The normal range for the basal metabolic rate was considered as -10 per cent to +10 per cent; that for the fasting blood cholesterol from 150 to 200 mg./c.c. The average basal figure in

TABLE I. TOXEMIA

NO.	PATIENT	DATE 1940	AGE	COLOR	MONTHS PREG- NANT	EDEMA	BLOOD PRES- SURE	KAHN	SERUM		PLASMA CO ₂ VOL. %
									PRO- TEIN GM. %	NaCl MG. %	
1	J. S.	1-10	28	B	7	+	198/106	++++	6.7	580	34
2	R. W.	1- 3	38	B	9	++	170/120	Neg.	4.6	610	--
3	E. C.	2- 7	29	B	9	+	160/110	++++	6.9	---	49
4	C. M.	2- 2	23	W	9	+	175/110	Neg.	6.0	643	43
5	M. B.	2-22	23	B	8	++	150/110	Neg.	6.4	---	41
6	C. W.	2- 1	24	B	9	+++	-----	Neg.	4.8	620	40
7	J. B.	2- 2	24	B	8½	++++	100/108	Neg.	6.7	620	33
8	C. M.	3- 7	32	B	8	+++	170/110	Neg.	4.6	620	37
9	M. M.	3- 7	15	B	8	++	200/130	Neg.	5.1	652	38
10	G. M.	5- 2	39	B	6	+	150/110	+++	6.1	---	33
11	A. B.	2-28	23	B	9	+	150/110	Neg.	5.6	565	34
12	J. R.	1-20	37	B	7	?	255/120	Neg.	--	---	--
13	R. L.	1-19	28	W	9	++++	155/110	Neg.	6.2	640	31
14	E. C.	1- 4	32	B	6	+	170/120	Neg.	6.7	---	--
15	C. W.	12-27 (1939)	38	B	9	++++	170/110	++++	--	---	36
16	C. S.*	2- 7	24	B	7	+	175/110	Neg.	6.0	643	43
17	W. L.	3- 7	16	B	8	?	175/115	Neg.	7.1	610	34
18	S. C.	4-21	32	W	7	+	200/120	Neg.	4.5	---	53

*Died.

†Delivered stillborn. Placenta retained. Died of peritonitis.

In the control group of 15 normal pregnant women, the average blood lead concentration of 0.031 mg. per 100 c.c. (± 0.0046 S.E.) agrees closely with the average normal value for both sexes from the general population. Individual values fall within normal limits with one exception. This patient was a gypsy admitted just before delivery with an incomplete and unsatisfactory history. Clinically she presented no evidence of toxemia.

Comparison of the mean values for blood lead in the toxemic and control groups by the method described by Student, using Fisher's² Table of t indicated that the difference is not due to chance. Failure to elicit history of unusual exposure strongly suggests that the source of the increased blood lead is from stores accumulated through casual daily contact and activated by metabolic disturbances arising during the course of pregnancy toxemia. This hypothesis is strengthened by the observation that in two patients (1 and 7), as well as in other toxemic cases not included in this series, elevated blood lead dropped to normal limits after delivery.

It is generally agreed that patients with an extrauterine infection should be treated conservatively. The only recent addition to our armamentarium is sulfanilamide. In the *Streptococcus hemolyticus* type of infected abortion, we have found the drug reduces the morbidity and has saved some of the hitherto hopeless cases.

Because we believe in the conservative treatment of both potentially and actually infected abortions of all types, it would seem advantageous to avoid even the slightest manipulation that might spread infection. On numerous occasions we have observed that the digital vaginal examination caused exacerbations in infected abortions. This procedure should be reserved only for cases of questionable diagnosis, or where immediate surgical intervention for localized pus is contemplated. Otherwise, the patient should be examined only after a five-day afebrile period. This, of necessity, would prevent an adequate pathologic classification of the infected case on admission; a point which we feel of no therapeutic moment.

REFERENCES

- (1) *Studdiford, W. E.*: Surg. Clin. North America 18: 511, 1938. (2) *Chandler, C. A., and Janeway, C. A.*: AM. J. OBST. & GYN. 38: 187, 1939.

LEAD MOBILIZATION ACCOMPANYING TOXEMIA OF PREGNANCY

T. V. LETONOFF, M.S., JOHN G. REINHOLD, PH.D.,
HELENA E. RIGGS, M.D., AND CLARENCE COHN, M.D.,
PHILADELPHIA, PA.

(From the Laboratories and the Department of Obstetrics, Philadelphia General Hospital)

IN THE course of a survey of lead concentration in tissue in disease, high values were found in kidney and pituitary of three women dying of toxemia of pregnancy. In these cases the fetal tissues also showed increased lead concentration. As a result of these findings, estimations of the lead content of blood and urine have been made on 18 patients with a clinical diagnosis of toxemia of pregnancy. This included 12 cases of pre-eclampsia, 1 case of eclampsia, 3 cases of nephritic toxemia and 2 of essential hypertension. Fifteen normally pregnant women in the same age group, and of similar economic status served as controls.

The salient studies in both groups are shown in Tables I and II. In patients with toxemia, the mean concentration of lead in whole blood was 0.053 mg. per 100 c.c. (± 0.0070 S.E.). This is well above the average established for normals by the method employed.¹ By this method, blood lead values for normal individuals average 0.0295 mg. per 100 c.c. (± 0.0029 S.E.) and findings of 0.060 or higher are considered indicative of excessive absorption or of lead mobilization. Eight toxemic patients showed blood lead concentrations above the range of normal established by Letonoff and Reinhold;¹ and by comparison with the control group, six presented significantly elevated values. Excretion of lead in the urine was measured in 3 of the cases of toxemia of pregnancy and was found to exceed normal limits in all cases. In 2 cases, this was associated with elevated blood lead; in the third, the blood lead value was normal.

sidered responsible for lead mobilization in pregnancy toxemias, since, in our experience, diabetic acidosis of comparable severity is infrequently associated with elevated blood lead concentrations.

The heavy drain on maternal calcium stores which normally occurs during the late months of pregnancy⁵⁻⁷ may act as an additional factor, simultaneously liberating lead stored in the skeleton. In toxemia of pregnancy in particular, the combined effects of decalcification and acidosis would exert a powerful action toward mobilization of the lead stores of the body.

While it is highly possible that other factors are concerned in the increase of blood lead in toxemia of pregnancy we have been unable to establish any such relationship in our studies. In particular, no association could be demonstrated between blood pressure, edema, gain in weight, serum protein, serum chloride or uric acid, blood sugar, blood urea nitrogen, hemoglobin or urinary changes, and the blood lead concentration (Table I).

TABLE II. NORMAL PREGNANCY

NO.	PATIENT	DATE	AGE	COLOR	URINE		BLOOD PRESSURE	BLOOD LEAD
					ALB.	CASTS		
		1940						
1	L. C.	2- 4	23	B	+	0	114/70	0.011
2	B. R.	2- 1	40	W	0	0	140/88	0.011
3	F. J.	1-28	18	B	0	0	122/75	0.013
4	L. S.	2- 1	21	B	+	0	140/95	0.015
5	R. N.	2- 3	26	B	0	0	140/100	0.020
6	H. H.	1-25	17	B	+	0	124/78	0.025
7	H. R.	1- 7	25	W	++	0	110/90	0.025
8	E. W.	2-15	25	B	0	0	112/78	0.034
9	V. T.	4- 4	19	B	0	Leuc.	100/60	0.036
10	E. Ma.	2-20	15	B	0	0	115/85	0.045
11	J. L.	2- 9	37	B	++++*		120/70	0.048
12	H. B.	1-23	40	W	0	0	140/90	0.056
13	M. C.	1-26	19	W	0	0	130/78	0.077
14	B. C.	4- 4	19	B	0	Epith.	135/90	0.025
15	E. Wm.	3-23	21	B	0	Leuc.	180/120	0.032
						++		

*After delivery.

In evaluating the significance of increased blood lead concentrations in toxemia of pregnancy, it should be emphasized that many of the symptoms characteristic of this condition, namely, hypertension, convulsions, headache, renal changes and visual disturbances, are also prominent manifestations of lead intoxication.

Hausmann and Perry⁸ have recently reported evidence of lead intoxication in a pregnant woman, associated with abnormal lead concentrations in the fetal tissues. Oliver⁹ and more recently Porritt¹⁰ and Milligan¹¹ have cited the greater prevalence of miscarriage and other complications of pregnancy among lead workers and in districts of the United Kingdom where drinking water contains lead in appreciable amounts. The susceptibility of the natives of the tropics to eclampsia after adopting the customs and dietary of the whites as reported by Peckham¹² suggests some relationship between eclampsia and the increased lead intake associated with civilization.

OF PREGNANCY

BLOOD HB. GM. %	SUGAR	BLOOD MG. %			URINE			HISTORY	DIAGNOSIS
		UREA N	URIC ACID	LEAD	LEAD	ALB.	CASTS, ETC.		
					MG. 24 HR.				
11	89	9	8.6	0.085	----	+++	R.B.C. Leuc.	Malaise, headache, convulsions*	Eclampsia
15.2	72	8	5.0	0.002	----	++++	Granular	0	Pre-eclampsia
9.6	54	10	5.0	0.011	----	trace	-----	0	Pre-eclampsia
10.0	87	9	5.3	0.038	----	+++	-----	Edema, vomiting	Pre-eclampsia
10.4	70	10	4.0	0.040	----	+ to	-----	Spots before eyes	Pre-eclampsia
						++++			
8.5	77	11	5.0	0.043	----	++++	-----	0	Pre-eclampsia
						to trace			
11.5	68	16	5.5	0.044	----	+++	-----	Headaches	Pre-eclampsia
8.1	77	9	2.6	0.054	----	++	-----	Headaches	Pre-eclampsia
9.6	56	10	4.3	0.062	----	++	R.B.C.	Spots before eyes, headaches	Pre-eclampsia
10.4	123	17	--	0.070		+++	Leuc. epith.	Dyspnea. 2 prev. stillbirths. Eye ground s neg.	Pre-eclampsia
8.1	70	16	4.0	0.075	----	trace		Spots before eyes	Pre-eclampsia
---	84	9	3.8	0.079	0.15	+++	R.B.C. Leuc.	Spots before eyes. Headache and vertigo	Pre-eclampsia
10.8	100	8	3.8	0.109	----	++	-----	0	Pre-eclampsia
10.0	72	8	3.6	0.064	0.189	0	0	0	<i>Essential Hy-</i> <i>pertension</i>
---	72	8	--	0.025	0.455	++++	-----	0	<i>Essential Hy-</i> <i>pertension</i>
---	87	20-10	3.8	0.001	----	++ to	Leuc.	0	Nephritis?
						+++			
12.4	70	8	4.0	0.039	----	+	-----	0	Nephritis?
14.0	84	35	--	0.115	----	++++	Leuc.	Diarrhea, headache, albuminuric reti- nitis with hyper- tensive changes. Gen. peritonitis†	Chronic pyelo- nephritis. Nephrolithia- sis. Chole- lithiasis.

However, it appears improbable that mobilization of lead is a causative or even a contributing factor in all cases of toxemia of pregnancy. Many patients in our series with typical clinical pictures of toxemia showed normal blood lead values. It is possible that the pregnancy toxemia itself, because of its complex nature and diverse etiology, may alter factors controlling lead absorption and mobilization. It is of considerable importance, however, that in this series one-third of the patients with toxemia of pregnancy showed blood lead concentrations as great as those encountered in moderately severe lead intoxication.

As Aub and his associates³ have previously shown for lead intoxication in general, we have noted a relationship in toxemia of pregnancy between concentration of blood lead and acidosis as measured by plasma carbon dioxide combining power (Table I). In most cases in our series the values for carbon dioxide combining power are lower than those given for normal pregnancy,⁴ and the high blood lead concentrations are, in general, associated with the lower values for carbon dioxide combining power. Such degree of acidosis alone can scarcely be con-

PROTHROMBIN CONCENTRATION IN PARTURIENT WOMEN AND THEIR NEWBORN INFANTS*

CARL T. JAVERT, M.D., AND ROBERT A. MOORE, M.D., NEW YORK, N. Y.
(From the Departments of Obstetrics and Gynecology and Pathology, New York
Hospital and Cornell University Medical College)

PROTHROMBIN determinations have become increasingly important in the medical management of surgical conditions, and more recently in the field of obstetrics and pediatrics, particularly in regard to hemorrhagic disease of the newborn. The original method of Howell for the determination of prothrombin using oxalated plasma and an excess of calcium has been improved upon by Quick, who uses an excess of calcium and thromboplastin. The titration method of Warner, Brinkhous, and Smith utilizes two steps; oxalated plasma freed of fibrinogen is diluted and prothrombin is converted to thrombin by the addition of thromboplastin; fibrinogen is then added, and the concentration of prothrombin is calculated and expressed in units or in percentage of normal. This method is far more accurate than the other two and has been used in the present study.

Having a satisfactory test at their disposal, Brinkhous, Smith, and Warner investigated the plasma prothrombin of infants. In a case of hemorrhagic disease, they found a value of 5 per cent on the seventh day of life. They studied the cord blood of 8 normal infants, and found values ranging from 14 to 39 per cent (average 26 per cent). Owen and co-workers using their method reported a further decrease in the amounts of prothrombin in the second to sixth days of life, when clinical bleeding is prevalent in cases of hemorrhagic disease. On the other hand, Quick, using blood from the internal jugular vein shortly after birth, found the prothrombin concentration to be nearly normal with his test, but observed a decline in the first days of life which had been shown earlier (1921) by Lucas. Owen and co-workers have shown that infants with low prothrombin values as determined by the Warner, Brinkhous, and Smith test, may have a normal prothrombin time according to the Quick test. They postulated that the quality of prothrombin may be a factor causing the discrepancy between the tests. In this way there may be compensation for the prothrombin deficiency at birth, by an increase in the speed of conversion of prothrombin to thrombin.

PRESENT STUDY

The prothrombin content of blood plasma was determined by the method of Warner, Brinkhous, and Smith, and the results expressed in percentage of normal adult controls. Twenty normal healthy pregnant women at term (during the winter of 1938 and 1939) were selected, and blood was obtained from the antecubital vein at the time of delivery, and from the fetal vessels of the placenta. In each instance, 4.5 c.c. of blood were placed into 0.5 c.c. of a 1.5 per cent solution of sodium oxalate. A second sample of blood was taken from the placenta for the

*This study was carried out under a grant from the John and Mary R. Markle Foundation.

While the significance of lead in the toxemia syndrome remains to be evaluated,* it seems not unlikely, in view of the toxic manifestations accompanying elevated blood lead in lead poisoning, that comparable blood lead values, resulting from mobilized lead, contribute to the symptom complex of toxemia in pregnancy. For this reason, we believe it is important to direct the attention of those engaged in study or treatment of the toxemias of pregnancy to the fact that such conditions are often associated with mobilization of lead.

SUMMARY

Toxemia of pregnancy is frequently accompanied by mobilization of lead as indicated by quantitative blood and urine lead determinations. Evidence suggesting that lead may be a causative or contributing factor in some cases of toxemia of pregnancy has been presented.

We acknowledge our indebtedness to Drs. Catherine Macfarlane and Philip F. Williams and their associates of the Department of Obstetrics for clinical data and for permission to report these findings.

REFERENCES

- (1) Letonoff, T. V., and Reinhold, J. G.: *Anal. Ed., Indust. & Engin. Chem.* 12: 280, 1940. (2) Fisher, R. A.: *Statistical Methods for Research Workers*, Edinburgh, 1936. (3) Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P.: *Medicine* 4: 1, 1925. (4) Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry* 1: Baltimore, 1931. (5) Oberst, W. F., and Plass, E. D.: *J. Clin. Investigation* 11: 123, 1932. (6) Mull, J. W., and Bill, A. H.: *AM. J. OBST. & GYNEC.* 27: 510, 1934. (7) Bodansky, M., and Duff, V. B.: *J. A. M. A.* 112: 223, 1939. (8) Hausmann, G. H., and Perry, M. C.: *Arch. Path.* 30: 226, 1940. (9) Oliver, T.: *Brit. M. J.* 1: 1096, 1911. (10) Porritt, N.: *Ibid.* 2: 92, 1931. (11) Milligan, E.: *Ibid.* 2: 222, 1931. (12) Peckham, C. H.: *Pennsylvania M. J.* 43: 909, 1940.

Southwick, W. E.: *Time and Stage in Development at Which Factors Operate to Produce Mongolism*, *Am. J. Dis. Child.* 57: 68, 1939.

Available data are not sufficient to allow a definite and final conclusion as to the exact time of the operation of the factor or factors which lead to the production of mongolism. On the basis of data on 58 cases of mongolism in dizygotic twins, the writer concludes that the causes of mongolism must reside in some factor or factors that cannot at any stage of development act directly on more than one ovum, zygote, or embryo. Since at all stages two or more ova, zygotes, or embryos may occur in exactly the same external environment, it is obvious that the condition can develop only from within the gametes, and so must be either chromosomal or cytoplasmic. The rarity with which two or more persons with the condition appear in one family makes it justifiable to conclude that mongolism is not produced by hereditary factors. The factors, therefore, are not considered to act at the time of the formation of the gametic chromosomes. The production of mongolism may be definitely associated with substances liberated from the ovum and from the spermatozoon, and mongolism may be the result of fertilization in which one or the other gamete was in an aged condition transitional to the nonfunctional or inactivable state. That the spermatozoa may thus be effective is shown by the abnormal sex ratio that occurs among those with mongolism. That the ovum may be similarly effective is shown by the definite relation between the mother's age and the frequency of production of mongolism. This study is based on records of 259 persons with mongolism.

J. P. GREENHILL.

*Work along these lines is in progress in this laboratory.

TABLE II. ADDITIONAL BLOOD STUDIES (CORD BLOOD) ON 20 NEWBORN INFANTS

CASE	RED CELL COUNT	HEMOGLOBIN (PER CENT)	CELL VOLUME (PER CENT)	ICTERIC INDEX (UNITS)
1	5,000,000	114	49	30
2	4,940,000	126	50	15
3	4,900,000	130	54	15
4	5,900,000	126	55	15
5	5,900,000	120	59	Hemolyzed
6	5,920,000	120	53	15
7	5,300,000	124	52	10
8	5,500,000	120	44	15
9	5,600,000	134	58	10
10	7,000,000	132	58	10
11	5,000,000	124	50	10
12	4,600,000	124	52	15
13	5,140,000	120	52	15
14	6,300,000	142	60	15
15			57	20
16	Not studied			
17				
18				
19				
20				
Average	5,500,000	126	54	15

DISCUSSION

Our determinations confirm the report of Brinkhous, Smith, and Warner in 1937, and have already been referred to in the literature by Hellman and Shettles, as a personal communication. Although a series of 20 cases is small, the consistency of the low prothrombin concentration of the infant as compared with that of the mother is rather striking. The infant has from one-third to one-fourth as much prothrombin as have the normal adult controls. The difference in the prothrombin of the blood plasma of the mothers and infants indicates that the molecule of prothrombin does not pass through the placental membrane. This suggests that the fetus produces its own prothrombin.

The comparison of prothrombin levels of the infant with adult values may be improper, and is not done with regard to other blood determinations on infants, such as hemoglobin, red count, and volume of packed cells; but normal values for the newborn have been established. Should not the low prothrombin concentration found in the newborn as indicated by the average value of only 23.6 per cent obtained in this study, or 26 per cent obtained by Brinkhous, Smith, and Warner be accepted as the normal for the newborn?

The low prothrombin values found in the infants may be due to the liver on the basis of hepatic insufficiency, which has been offered by Waugh and his co-workers as the explanation for the development of hyperbilirubinemia and icterus neonatorum. In this respect the fetal circulation is perhaps of great significance since the ductus venosus permits blood to by-pass the liver by emptying into the inferior vena cava. After the umbilical cord is ligated, several days must elapse in order for the portal circulation and liver to assume the production of pro-

determination of red cell count, hemoglobin, volume of packed cells, and the icteric index. The cell volume of the mothers had been determined on admission to the delivery floor.

TABLE I. PROTHROMBIN IN 20 NEWBORN INFANTS AND THEIR MOTHERS AT DELIVERY
(Titration Technique)

CASE	PER CENT OF ADULT NORMAL		WEIGHT OF INFANT (GRAMS)	BLOOD LOSS THIRD STAGE LABOR C.C.	ADMISSION CELL VOL.
	MOTHER	INFANT			
1	100	22	3650	140	35
2	100	25	3770	90	37
3	90	35	4100	50	37
4	70	25	3090	20	32
5	80	15	3550	180	38
6	70	25	3540	70	46
7	60	30	3930	290	30
8	100	35	3880	195	33
9	50	10	3570	300	37
10	70	30	3560	270	38
11	25	10	3300	45	36
12	60	20	3680	250	33
13	55	25	3860	120	37
14	100	25	3090	100	35
15	70	15	3940	75	35
16	70	25	3450	500	37
17	85	45	4060	160	36
18	75	15	3330	75	40
19	100	25	3700	300	38
20	100	22	3300	450	36
Average	77.8	23.5	3617	165	36

Table I shows the average prothrombin level in the mothers as 77.8 per cent (range 25 to 100 per cent of the adult normal), and the average volume of packed cells as 36 per cent; the latter value is considered a normal figure for pregnant women at term. It will be recalled that the average is about 42 per cent in non-pregnant patients, so that the lower value in pregnancy is probably due to an associated hydremia. The mothers had an average blood loss of 165 c.c. (range 20 to 500 c.c.). The patient in Case 11 had a prothrombin concentration of 25 per cent of the normal, just on the hemorrhage border line for patients with jaundice, and had a blood loss of only 45 c.c., during the third stage of labor.

As shown in Table I, the average prothrombin concentration in the infants was 23.5 per cent, with a range from 10 to 45 per cent, which is one-third to one-fourth as much as the amount present in the mothers. The infants were all full term, with an average weight of 3617 Gm. No infant developed hemorrhagic disease. This is of further significance in Cases 5, 9, 11, 15, 18, with unusually low prothrombin values of between 10 and 15 per cent of the adult normal.

The volume of packed cells, hemoglobin, red cell count, and icteric index are shown for 14 of the infants in Table II. The red cell count averaged 5,500,000 per c.mm., and the average hemoglobin was 126 per cent, using the Hellige hemometer (14.5 Gm. = 100 per cent). These findings are within the normal range for the newborn, but considerably higher than are found in the adult. The volume of packed cells was 54 per cent, which is higher than the adult average of 42 per cent. The icteric index was also elevated to an average of 15 units, which is not unusual for a normal newborn infant. The low concentration of prothrombin in the infants is not due to plasma dilution. Is it due to failure of formation?

Cases 1, 4, 6, 7, 8, 16, 18, with an average icteric index of 17 units (excluding No. 16, and 18 on whom no determination was made) had clinical evidence of jaundice.

OPERATION FOR UTERINE RETRODISPLACEMENT AND PROLAPSE BY REDUCTION AND ATTACHMENT OF THE ROUND LIGAMENTS

K. P. A. TAYLOR, B.S., M.D., F.A.C.S., PUERTO ARMUELLES, PANAMA

ONE must advance an adequate reason, if not an excuse, for introducing another operation for retrodisplacement of the uterus. In the present instance, dissatisfaction with the admittedly infrequent shortcomings of the standard operations prompted the development of a modified technique which possesses definite advantages. I do not share with Dannreuther¹ his partiality for the Baldy-Webster and Gilliam-type operations, but agree rather with Graves'² statement that no operation which depends upon shortening of the round and uterosacral ligaments can be depended upon to withstand gestation and parturition. In addition, the Baldy-Webster maneuver predisposes to the formation of adhesions in the cul-de-sac which may readily defeat the operation's purpose; furthermore, the reported incidence of herniation through the broad ligament openings is now so convincing that the technique should be employed only with the greatest care and proper misgiving. Similarly, the Gilliam operation has the following defects: The creation of three pockets between the round ligament emplacements and at the sides which favor herniation and ileus; in the presence of inflammatory disease, a fixed barrier or shelf vertically dividing the pelvis, may result from adherence of the round and broad ligaments and the fundus to the abdominal wall; in addition, many patients complain of pain in the region of the internal ring which persists for several months after the Gilliam type operation. We, therefore, prefer the principles set forth by Olshausen, and advanced by Graves. In the Olshausen operation, the thickest, most dependable part of the round ligaments, close to the corpus, is fixed to the anterior abdominal wall by a permanent suture through the peritoneum, muscle, and fascia. This operation is, in effect, a ventral fixation of the uterus, since the segment of round ligament employed must be considered a projection of the corpus. Because, as Dannreuther has indicated, many suspensions became fixations, we prefer to discard both terms in favor of the more inclusive name, attachment.

OLSHAUSEN OPERATION

The disadvantages of this procedure may be enumerated as follows: Two-point fixation, with the resulting three interspaces which invite intestinal incarceration; restricted mobility of the uterus and reduction of bladder space, as mentioned by Dannreuther and others, which is common to all operations for retrodisplacement or prolapse; reduction of bladder space which cannot occur if the attachment is sufficiently high

thrombin and the excretion of excessive bilirubin. In the meantime, hyperbilirubinemia occurs with and without clinical icterus, and a further lowering of the "physiologic hypoprothrombinemia" takes place in the first days of life as shown by Warner and co-workers, and by Owen and his associates.

CONCLUSIONS

1. The prothrombin concentration of 20 parturient women at term, and of the cord blood of their infants was determined by the method of Warner, Brinkhous, and Smith. The concentration expressed in per cent of the adult normal was 77 for the mothers, and 23 for the infants. This difference suggests that the prothrombin molecule does not cross the placental membrane.

2. Readings as low as 10 to 15 per cent of the adult normal were observed in several infants without evidence of hemorrhagic disease. The critical levels in the newborn must be determined by further study.

3. One mother had a low value distinctly in the bleeding range for jaundiced patients, with a minimal blood loss in the third stage of labor.

4. The low levels in the infant are evidently not due to dilution, since the volume of packed cells was not reduced, and may instead be the result of failure of production on the basis of liver insufficiency. The further reduction occurring in the first days of life is probably on the same basis.

5. In making statistical comparison of prothrombin concentration as determined by various investigators, attention must be given to the source of blood (cord or jugular), the day of life, and the method used for the determinations. This will do much to clarify the present conflicting situation as to whether the low prothrombin levels at birth are normal.

6. Consideration must be given to the quality as well as the quantity of prothrombin. The speed of convertibility may explain why less than one infant in one hundred develops hemorrhagic disease. The low prothrombin level in the cord blood at birth may predict such a tendency.

7. Hypoprothrombinemia and hyperbilirubinemia of the newborn are probably caused by hepatic insufficiency. The importance of the patent ductus venosus in this connection was emphasized.

REFERENCES

- (1) *Brinkhous, K. M., Smith, H. P., and Warner, E. D.*: Am. J. M. Sc. 193: 475, 1937. (2) *Hellman, L. M., and Shettles, L. B.*: Bull. Johns Hopkins Hosp. 65: 138, 1939. (3) *Lucas, W. P., et al.*: Am. J. Dis. Child. 22: 525, 1921. (4) *Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P.*: Proc. Soc. Exper. Biol. & Med. 41: 181, 1939. (5) *Quick, A. J., and Grossman, A. M.*: Am. J. M. Sc. 199: 1, 1940. (6) *Idem*: Proc. Soc. Exper. Biol. & Med. 40: 647, 1939. (7) *Quick, A. J., Brown, M. S., and Bancroft, F. W.*: Am. J. M. Sc. 190: 501, 1935. (8) *Warner, E. D., Brinkhous, K. M., and Smith, H. P.*: Am. J. Physiol. 114: 667, 1935.

the group which became pregnant (A) was -17 per cent, and the fasting blood cholesterol 256 mg./c.c. The highest rate noted was -10 per cent and the lowest -28 per cent, the cholesterol varying from 155 mg./c.c. to 400 mg./c.c. In Group B, the average basal determination was +9 per cent with variations ranging between a +3 per cent and a +14 per cent. The fasting blood cholesterol averaged 183 mg./c.c., with variations between 175 mg./c.c. and 200 mg./c.c.

The fact that a normal basal was found was not accepted as reliable assurance that thyroid function was normal,¹⁹ nor a low basal to indicate necessarily hypothyroidism (Litzenberg³). For a proper diagnosis, the basal was considered together with the cholesterol level, the physical findings and the subjective symptoms. Thus 5 cases in Group A (2, 3, 5, 6, and 8) must be considered as suffering from a mild degree of true clinical hypothyroidism, while the remaining 4 (1, 4, 7, and 9) present sufficient evidence to warrant a diagnosis of subclinical hypothyroidism. In Group B, only a diagnosis of normal thyroid function could be made, since all findings were well within the normal range.

Tubal Insufflation.—VanTongeren,²⁰ Rubin⁹ and others have demonstrated that the mere dilatation of the cervical canal, the insertion of a sound into the uterus, or the passage of gas through ostensibly normal tubes is sufficient to relieve sterility. Therefore the number of patency tests was limited to a minimum. In the group which became pregnant, insufflation was done only one time in only 6 of the 9 cases. Of the remaining 3, one (6-A) was not treated for sterility, one (7-A) became pregnant before the test could be done, and the third refused on the ground that she had undergone the test about a year previously and had been ill for several weeks thereafter. The patients in Group B, likewise, were insufflated only once, with one exception (1-B) where the test was repeated at the end of the first year of treatment.

In neither group was any abnormality found. Little or no difficulty was experienced in the insertion of the cannula, and the passage of gas through the tubes was accomplished without excessive pressure. In all cases the peristaltic action of the tubes was normal.

Therefore, it was felt that tubal insufflation was not a factor in producing pregnancy, since both groups received approximately equal amounts of insufflation; since no abnormal findings were noted in the tests; and since 3 patients who were not insufflated conceived.

Duration of Sterility Following Thyroid Therapy.—Omitting one case (2-A), the average duration of sterility following thyroid therapy was six months. Case 2-A demonstrated the fact that a sufficient quantity of thyroid must be given. She had been taking 12 gr. of thyroid daily for eleven months without effect. Through an error, the dose was doubled without untoward results. After receiving 24 gr. daily for 2+ months, conception occurred.

In the second group (B) the longest any patient was under treatment was two and one-half years, with an average for the entire group of eighteen months.

Prenatal Course, Labor and Delivery.—Of the 9 conceptions, 7 carried to viability. Two aborted, one (5-A) after an automobile accident in the fifth month, and one (6-A) induced in the third month. Two (4-A) (9-A) delivered prematurely, three weeks and one month, respectively.

The patient in Case 2-A developed a true hypertensive toxemia in the seventh month, but was sufficiently controlled so that she was able to carry to term. Case 3-A attempted to abort in the third and fourth months, but was stopped by use of morphine and progesterone. This patient also had a prolonged labor, which was followed by a severe post-partum hemorrhage.

SUMMARY

Sixteen sterile women, free of all pathologic and infectious processes, were given desiccated thyroid extract in tolerance doses, regardless of the thyroid status of the individual. Nine of the entire group became pregnant; 7 remained sterile. In the 9 cases where pregnancy occurred, only 7 carried fetuses to viability, 2 aborting as the result of external trauma.

on the parietes—a point emphasized in the operation to be described. A fourth objection to this admirable operation is its failure to reduce or shorten the round ligaments.

REDUCTION-ATTACHMENT OPERATION

Our objective has been a method which permits reduction or shortening of the round ligaments, utilizes the strong proximal portions of the round ligaments, and allows attachment of the uterus at a single point to the abdominal wall. This we have evolved by attachment of the corpus through the direct medium of the round ligaments. Secondary objectives were facility of operation and use of a single suture for the completed procedure.

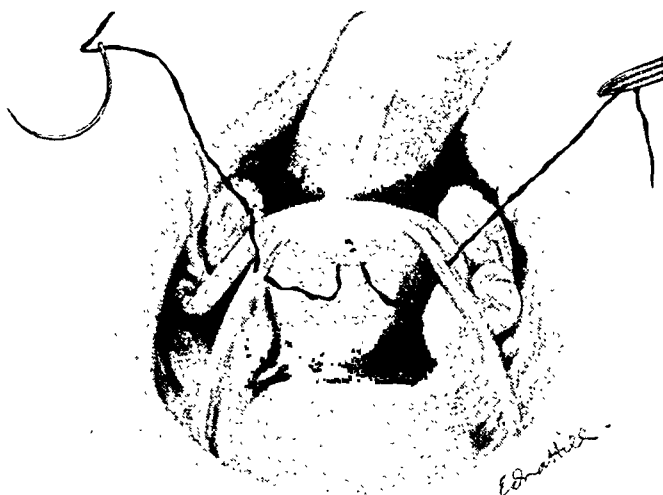


Fig. 1.—Suture of four strands of No. 24 cotton thread passed through round ligaments 1.5 cm. from corpus and through a segment of corpus.

OPERATIVE TECHNIQUE

A 14-inch suture composed of four strands of No. 24 plain black spool cotton thread (3) (or an equivalently strong single silk or linen suture) is passed through a round ligament 2 cm. from the corpus, through a 1 cm. segment of the uterus 2 cm. below its fundus, and through the other round ligament at the same level. The suture ends, of equal length, are tied in a single square knot which brings the ligaments together at a point of attachment. The needle is then introduced through the round ligaments at the midpoint from corpus to internal rings, and the suture again tied to the original end. Thus the ligaments are reduced by half. Clamps are placed on the peritoneal edges 6 cm. above the lower wound angle. The needle is passed from within-out through peritoneum, muscle, and fascia on the left side of the incision, and returned to the abdomen from without-in through fascia, muscle, and peritoneum of the right side. The suture is then tied to the original long end within the peritoneal cavity, thus completing the attachment. It is seen that the directional stress or support is through the strongest units of the round ligaments to the corpus itself. The 4-strand cotton suture can be depended upon for permanency. Adherent attachment will also occur.

In prolapse, the usual plastic vaginal repairs are done first. We have not found it necessary to plicate or sew together the uterosacral ligaments. In severe prolapse, the attachment is made as high as the fundus can be extended, without tension. Removal of all or part of the corpus will frequently make

possible a still higher relative attachment in third and fourth degree prolapse with relaxed abdominal musculature.

It is indicated that this operation does not aim at antelexion. The attachment is on the anterior surface of the uterus, so that growth during gestation will not be hampered. Since the attachment-suture closes and frequently inverts

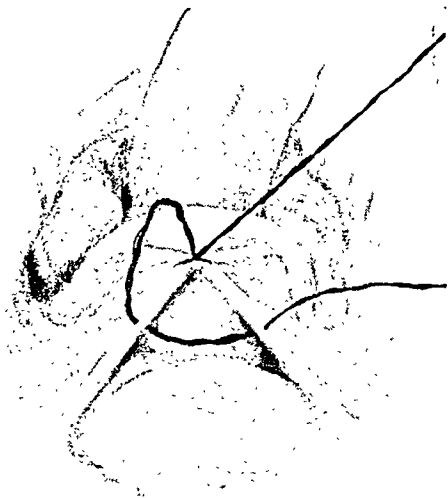


Fig. 2.



Fig. 3.

Fig. 2.—Suture tied and passed again through round ligaments at midpoint to internal ring.

Fig. 3.—Second tie. Point of uterine suspension is 2.5 cm. below top of fundus.

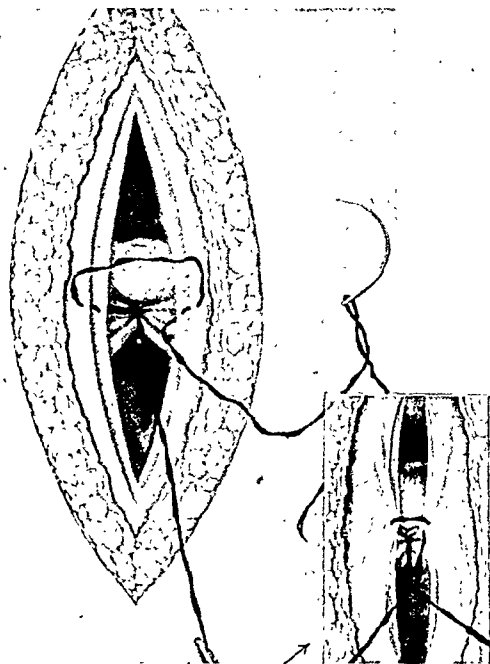


Fig. 4.—Same suture passed through peritoneum and fascia on both sides of incision 6 to 8 cm. above lower angle of wound. *Inset:* Suture tied to original long end within the abdomen.

the peritoneum at the point of fixation, unusual care must be exercised in sewing the peritoneal edges to prevent the formation of a cleft or defect which would predispose to ventral hernia. Presence of the bulk of folded round ligaments at the attachment point emphasizes the need for meticulous closure.

RESULTS OF OPERATION

This technique has been developed over a four-year period in 120 patients. In its present form it has been used for two years, the quadruple cotton suture for one year. Our opportunity for re-examination is necessarily limited. No failures have been detected. The few patients (6) subsequently seen in parturition and puerperium have not had dystocia due to operation and have not had recurrence of retro-displacement. No sinuses have resulted. The postoperative and convalescent courses in cases not complicated by other pelvic pathology have been relatively comfortable.

RÉSUMÉ

1. A simple, rapid technique is presented for reduction of round ligaments and single-point attachment of the uterus. Pocket formation of the Gilliam and Olshausen operations is avoided.
2. This operation has the merits of the Olshausen procedure and apparently none of its disadvantages.
3. A single 4-strand cotton suture is utilized.

REFERENCES

- (1) *Dannreuther, W. T.*: J. A. M. A. 113: 1609, 1939. (2) *Graves, W. P.*: Gynecology, ed. 4, Philadelphia, W. B. Saunders Co. (3) *Taylor, K. P. A.*: Am. J. Surg. In press.

UNITED FRUIT COMPANY HOSPITAL

THE NAUSEA AND VOMITING OF PREGNANCY DUE TO ALLERGIC REACTION

A STUDY OF 192 CASES

J. WILLIAM FINCH, M.D., HOBART, OKLA.

(From the Department of Obstetrics of the University of Oklahoma School of
Medicine and University Hospitals)

THIS report is a summary of work done subsequent to a publication in 1938,¹ theorizing that the nausea and the vomiting accompanying pregnancy are due to an allergic reaction of the patient to the secretion of her own corpus luteum graviditatis. A report of 192 cases is presented to substantiate this theory further.

From one-half to two-thirds of all obstetric patients experience nausea and vomiting in some degree during the first trimester. The symptoms may vary in severity from the mild case, so frequently seen, in which there is morning sickness, with or without vomiting, to the moderate case, in which there are nausea all day long, frequent vomiting, and extreme discomfort for weeks. A few cases will advance to a true hyperemesis gravidarum with a definitely serious prognosis.

I believe the patient presenting nausea and vomiting of pregnancy has inherited an allergic tendency and has become sensitive to her own corpus luteum secretion during her menstrual life or from the corpus luteum of a previous pregnancy. I believe the symptoms of nausea and vomiting develop as an allergic reaction to the secretion of the corpus luteum of pregnancy and disappear after the gland ceases to feed its secretion into the patient's body in such abundance. The results of this research strongly indicate the presence of a luteal secretion other than progesterone which is responsible for this allergic manifestation.

The corpus luteum, with impregnation, continues to develop instead of taking on the customary retrogressive changes during and after menstruation. The corpus luteum of pregnancy develops to a size much larger than the false corpus luteum; the colloid is more abundant in the organ, and the granulosa cells are larger than before pregnancy.²

Considering that the development of the nausea and vomiting and the development of the corpus luteum of pregnancy occur at the same time and that the time of disappearance of symptoms coincides with the time of retrogressive changes in the gland, patients with nausea and vomiting of pregnancy were given intradermally injections of various corpus luteum extractions. Intradermal reactions developed in direct proportion to the degree of nausea and vomiting present. Likewise, patients treated with desensitizing doses of these extractions were relieved of their symptoms.

To avoid confusion in the following case reports, the term "progestin" will be used to indicate the natural hormone of the corpus luteum as it occurs in partially purified extracts. The term "progesterone" will be used for the synthetically produced pure hormone ($C_{21}H_{30}O_2$) dissolved in oil.

TECHNIQUE OF INTRADERMAL TESTS

The technique of intradermal testing for sensitivity was to cleanse the skin with alcohol and to inject intradermally from 0.02 to 0.03 c.c. of the test solution. Twenty to thirty minutes later reactions were recorded, calibrating them from negative to plus four, according to the size of the wheal and the surrounding erythema produced, just as in intradermal injections of any food, drug, pollen extract, or animal dander to determine a patient's degree of sensitivity. The majority of tests were made on the volar surface of the forearm. Numerous products were used in the skin tests, but the most satisfactory was found to be progestin in sterile cottonseed oil, as this oil is less irritating when injected intradermally than is oil of sesame, almond oil and peanut oil used in some commercial products. A control test was made in each case by injecting intradermally a like amount of the sterile oil used, to rule out cases of sensitivity to the oil alone. Many of the cases were rechecked, using a glycerin extraction of the corpus luteum, but this was given up as impractical as the solution was unstable and the glycerin was very irritating to some skins.

Since it is known that the placenta also secretes progesterone and that the daily output of urinary pregnanediol rises abruptly during the second and third trimesters, we must assume that these patients presenting nausea and vomiting are sensitive to some other luteal secretion than progesterone, else they would become more and more nauseated as their

pregnancy advances. Because of this fact, patients were intradermally tested with synthetic progesterone in oil and with progestin in oil. Intradermal reactions to the natural progestin were in almost every case directly proportional to the degree of nausea and vomiting the patient presented. Reactions to the intradermal synthetic progesterone were negative in most cases and followed no proportional ratio to the degree of the symptoms.

Commercial products of progestin are prepared by alcoholic extraction of corpora lutea and purification of the oil. The estrins are removed by subsequent chemical treatment. This product is assayed for its progesterone content alone but must contain some other hormone to explain the results obtained in this research. I do not believe that the allergen is the gonadotropic hormone of pituitary origin or of chorionic origin, else we would have, with the former, hyperemesis with many cases of natural and surgical or radiation menopause and with the latter would have hyperemesis with chorionepithelioma, for in these conditions the gonadotropic hormone level increases tremendously, even above that of the nausea and vomiting of pregnancy.

Injections of large doses of natural progestin into rabbits failed to give a positive Friedman test.

As a further control of the intradermal tests, 20 patients with skin sensitivity to progestin were also tested with intradermal estrogen and with the gonadotropic fraction from pregnant urine. Skin reactions to these products were essentially negative and in no ratio to the degree of nausea and vomiting present.

CASE REPORTS

Series A.—A series of 42 pregnant patients with nausea and vomiting, and in the first trimester, was tested for skin sensitivity to progestin. Ages varied from eighteen to thirty-nine years. Parity range was from primipara to nonigravida. Menstrual histories were essentially normal. A very high percentage of patients had been severely nauseated with previous pregnancies. Their skin reactions to progestin varied in direct proportion to their degree of nausea and vomiting, from one-plus to four-plus. Sixteen per cent gave a history of personal allergy (hives, hay fever, asthma, migraine, or urticaria), and 25 per cent of them gave a history of allergy in the family.

Twenty-two of these patients were observed to the termination of the pregnancy. Twenty had normal children at term, 13 being male and 7 female. Two had premature births, one at four and one at six months' gestation. One had a threatened abortion at six months. There were no cases of toxemia of late pregnancy.

Series B.—There were five nonpregnant multiparas with a history of moderate to severe nausea and vomiting with previous pregnancies, and with no history of family allergy. Two had a history of personal allergy, who gave two-plus and three-plus skin reactions to progestin.

Series C.—Four virgins, with no history of family allergy, one with premenstrual migraine, and two with premenstrual nausea, gave two- and three-plus skin reactions to progestin intradermally.

Series D.—Twenty-three pregnant patients in the first trimester, who had no nausea or vomiting with the present or any previous pregnancy, were tested intradermally as outlined above. Ages varied from 18 to 38 years and the parity range

was from primipara to quintipara; 4.3 per cent gave a history of family allergy. None had a history of personal allergy. One patient had a one-plus skin reaction and 22 were negative.

Series E.—Five nonpregnant multiparas with a history of having had no nausea or vomiting with previous pregnancies, no history of menstrual abnormality, and no history of allergy, either personal or familial, had negative skin reactions to progestin intradermally.

Series F.—Six virgins with no history of menstrual abnormality or allergy had negative skin reactions to progestin.

Series G.—If the theory upon which this research is based is true, girls before puberty, theoretically, should react negatively to intradermal corpus luteum extracts, never having had any luteal function. Fifty-six girls, chosen at random from pediatric wards, none seriously ill, were tested in the manner described. Ages ranged from two months to thirteen years. All but three patients were less than 10 years of age. Seven children had one-plus reactions and 49 were entirely negative in reaction.

Series H.—Fifty-one cases of moderate to severe nausea and vomiting of pregnancy were tested intradermally with progestin for sensitivity and treated along the lines of allergic desensitization to the corpus luteum hormone using graduated doses of progestin in oil intramuscularly. Fifty of the cases were white women, one a negress. All were in the first trimester of pregnancy. Cases were divided equally among charity patients and private patients of fair to excellent financial and social status. About half of the pregnancies were desired and half unwanted. Patients varied in age from 17 to 42 years and in parity from primipara to octipara. All had essentially normal menstrual histories except a few cases of premenstrual migraine, premenstrual nausea, and dysmenorrhea.

Fourteen cases were classified in severity as four-plus (nauseated all of the time and vomiting all ingested food and fluid). Twenty-one were classified as three-plus (nauseated all day and vomiting three or four times daily). Sixteen were classified as two-plus (nauseated all day and vomiting none to two times).

TREATMENT

Patients were treated with some variation but the average was to begin with one half international unit of progestin in oil. One day later one unit was given. Treatment then followed at forty-eight- to seventy-two-hour intervals until the patient stopped vomiting, increasing the dose gradually to three or four units if necessary. When the vomiting ceased, the dose was not further increased and the interval between doses gradually lengthened to five days. As soon as nausea had disappeared, the dose was somewhat reduced and continued at five- to seven-day intervals for two or three doses. Some patients responded so promptly that the dose was not increased beyond one and one-half units. The patient's response to treatment directed the rapidity and degree of increase and decrease of dosage. A few patients were found who were apparently very sensitive to the drug and could not tolerate large doses. In these cases, too great an increase would markedly increase the symptoms for a few hours. Generally speaking, the patients with four-plus skin reactions required larger doses and a greater number of total doses for relief than those with lesser skin reactions.

The average total amount of the drug used was 9.05 international units per patient, given in an average of 7.3 total doses. Results were excellent in 44 (87.4 per cent) of the cases, fair in 2 cases (3.9 per cent), and poor in 5 cases (9.8 per cent). The average length of time from beginning treatment until all vomiting ceased was 4.8 days. The longest time was nine days. The average length of time from beginning treatment until relief from nausea was 8.05 days. The longest time was nineteen days.

Twenty-six per cent of the patients in this series gave a history of personal allergy other than the nausea and vomiting. Thirty-six per cent gave a history of allergy in the family. Forty patients were observed throughout their pregnancy. Of these, 4 had premature births, 3 at three months' gestation and one

had a Voorhees bag induction at seven months' gestation because of a severe eclampsia. Eighteen babies were females and 22 were males. There were no maternal deaths and no fetal deaths except these 4.

Of these 51 patients, 10 were given synthetic progesterone at the beginning of treatment. Nine showed no improvement and one had very slight improvement after one week. Treatment was then changed to natural progestin without telling the patient of the change. There was marked improvement in a few days in each patient. Another 10 patients were started on treatment with sterile oil injections. One of these patients showed a very slight improvement and 9 no improvement after one week. Again, without telling the patient, the treatment was changed to progestin with marked improvement in a few days.

Eight patients had had phenobarbital, one had had intravenous calcium gluconate and another had had six doses of an unknown drug hypodermically before treatment as described above was begun. None had had relief from their symptoms. The remaining 43 patients had had no treatment. No treatment other than that described was used in any of these cases. Forty of the series were treated as ambulatory patients. Eleven were kept in the hospital in order that they might receive their treatments and be observed accurately. Patients were kept in undarkened rooms, were allowed visitors and radios, and were sent general diet trays. Ambulatory patients were instructed to do and eat as they desired.

Four of this series were given intradermal tests before pregnancy occurred. Positive reactions were obtained in direct proportion to the degree of nausea and vomiting that developed when pregnancy ensued, although the patients were not told what the tests indicated.

Nineteen patients had four-plus skin reactions, 17 had three-plus reactions, 13 two-plus reactions, 1 a one-plus reaction, and 1 a negative reaction. The patient with the negative reaction was definitely psychic and the one-plus reaction was in a patient with a pituitary syndrome (basophilic adenoma), who although the skin reaction was slight, was greatly benefited by the treatment. With few exceptions the skin reactions were directly proportional to the severity of the symptoms in each case.

Twenty patients from Series "A" were treated with synthetic progesterone in doses similar to that used in Series "H." Four of these patients were slightly improved and 16 had no improvement whatsoever.

Of the 5 patients in Series "H" who had no improvement from the treatment, one was a known neurotic who had had severe vomiting with three previous pregnancies. Her skin reaction was negative and treatment gave no relief. Psychic treatment effected a rather spectacular cure. Two of the case reports were pregnancies in the same patient on successive years. Her skin test was three-plus. She had intense nausea but was seldom able to vomit. Treatment did not effect any improvement. Psychotherapy failed to be of any value after the other treatment was discontinued. Symptoms subsided in the fourth month of pregnancy.

The fourth patient had a positive skin test but was very neurotic and informed us she could tell the exact date on which she would cease vomiting. She missed her calculations two days. The remaining patient came to the hospital in a state of starvation, acidosis, and avitaminosis, having vomited for five weeks with almost continuous vomiting for four days. This patient had to have fluids, glucose, vitamin concentrates, and sedatives to control her vomiting. She was also given progestin and had no reoccurrence of her trouble. She would have had no reoccurrence anyway in all probability as she was then entering her fourth month of pregnancy.

Of the 2 patients with only fair results, one, an earlier case in the series, had inadequate dosage. The other did not respond well although treatment was adequate. Both patients had four-plus skin reactions. Vomiting was controlled in each case but the nausea continued until the fourth month of pregnancy.

An interesting notation was that about 40 per cent of the patients in Series "A," the untreated series, complained as late as five or six weeks after the intradermal injection that when they became nauseated severely the area of

intradermal injection again became irritated and formed a wheal with a surrounding erythema and intense itching. This reoccurrence of the positive skin test occurred in all 4 of the patients in Series "C," five or six days following ovulation. I know of no way to explain this other than that the solution injected, being an oily one, is absorbed very slowly and part of it remains in the skin for a protracted time, causing a reoccurring positive test when the corpus luteum secretion of the patient is more abundant.

COMMENT

From these results I believe this method of diagnosis from intradermal testing will prove of value in eliminating the small percentage of psychic cases of vomiting from those definitely ill. By skin tests one may prognosticate which patients will suffer from nausea and vomiting early in pregnancy, or perhaps, even before pregnancy occurs and may use this method of treatment as a preventive measure. I believe this method of treatment, if begun early in the nausea and vomiting, will prevent practically all of the severe cases of hyperemesis too frequently seen, in addition to relieving countless thousands of women each year from a most uncomfortable period of weeks of nausea with or without vomiting.

Although desensitization to progestin can prevent hyperemesis and can cure the earlier cases, I doubt if it will be sufficient in itself to cure the patient who is not seen until late in pregnancy, for here we are dealing with a patient who has missed her early treatment and is now sick from starvation, acidosis, avitaminosis, and severe dehydration. No doubt, it will be necessary to replace fluids and vitamins and give sedatives to these patients; however, if still in the first trimester, desensitization to her corpus luteum may be a useful adjunctive treatment. Most of these late cases are entering the second trimester and as soon as this starvation and dehydration is remedied, the patients will be free from nausea and vomiting, as the corpus luteum has then begun to regress and its secretion has lessened or disappeared—an analogous condition to the hay fever sufferer following the first heavy frost. This fact alone is perhaps the answer to why patients who have vomited for weeks finally are taken to the hospital and recover spectacularly with replacement of fluids, glucose, and with sedatives. They were sick, by the time of hospital admission, not from an allergic nausea and vomiting of pregnancy but from a secondary condition of starvation produced by the nausea and vomiting.

This treatment is economical, the cost of the drug necessary for treating the average case being less than ten dollars and the duration of the treatment comparatively short. It is without danger of ill effects.

The results, both diagnostic and therapeutic, from natural progestin versus the lack of results using synthetic progesterone would indicate strongly the existence of another hormone of the corpus luteum, other than progesterone, in the products made from luteal extractions, now commercially available. It will be interesting to see what will be learned by further analysis of these luteal extractions.

In summarizing the literature, there is further evidence that the nausea and vomiting of pregnancy is allergic. Hirst³ was the first to associate the nausea and vomiting of pregnancy with the function of the corpus luteum. Duplication of his work has not produced uniform results, however, because the gland extracts available until recently were unstandardized and of inadequate potency. It can be assumed that he was able to relieve his patients, not by giving them a secretion in which they were deficient, as he theorized, but by desensitizing them to some degree and relieving them of their allergic reaction.

Saxon and Stoll⁴ report 75 patients treated with autohemotherapy, theorizing that the small amount of blood injected into the tissues is in the nature of a desensitizing process to a certain toxin which is elaborated and absorbed into the blood stream of the pregnant woman. In their series, the serum of the pregnant patient probably contained sufficient luteal hormone to effect a desensitization when injected.

Freeman, Melick and McClusky,⁵ and Kotz and Kaufman⁶ report good results with the administration of adrenal cortex, both orally and hypodermically. It is not unlikely that results from administration of this substance are brought about by treatment of the allergy of the patient alone, as Pottenger and Pottenger⁷ report 50 children with asthma treated successfully for one year by the use of adrenal cortex.

Hawkinson^{8, 9} reported 150 patients treated with estrogen with good results. He gave severely ill patients daily injections of 10,000 units of theelin in oil. Numerous observers have proved the depressing activity of the estrogens on anterior pituitary function, which no doubt explains the results with this therapy, i.e., depressing the luteinizing factor of the pituitary should decrease the secretion of the offending hormone of the corpus luteum. As further proof of this explanation, Brindeau, Hinglais and Hinglais¹⁰ report 15 patients with nausea and vomiting of early pregnancy in which the titer of the gonadotropic hormone (prolan B) of the blood was above normal in direct proportion to the degree of the symptoms. With cure of the nausea and vomiting, all titers returned to normal.

In hyperemesis gravidarum, Siebke¹¹ was unable to detect any abnormality in concentration of the estrogenic substance of the blood. Thus, it seems that this treatment as recommended by Hawkinson, using estrogen, is not without danger of inducing abortion. Costa and Cantilo¹² report that abortion frequently followed administration of large amounts of theelin when corpus luteum was not subsequently used.

SUMMARY

1. The nausea and vomiting of pregnancy develop at the same time at which the corpus luteum of pregnancy reaches an appreciable size. The symptoms disappear at about the time the gland is known to begin retrogressive changes.

2. In 98 patients with nausea and vomiting of pregnancy in varying degrees, a cutaneous reaction directly proportional to the degree of the severity of the symptoms developed when injected intradermally with from 0.02 to 0.03 c.c. of progestin (natural) in oil.

3. A control series of patients who were not nauseated and in the pregnant state gave negative cutaneous reactions when tested in a like manner.

4. A series of young girls, before puberty, likewise gave negative reactions to intradermal progestin.

5. 91.2 per cent of 51 patients treated with progestin in oil along the lines of allergic desensitization were relieved of their symptoms.

6. A control series of patients treated and skin tested with synthetic progesterone in oil failed to react or to be relieved of their symptoms.

7. A high percentage of the patients with nausea and vomiting of pregnancy either had other diseases of allergy or gave a family history of allergy.

CONCLUSIONS

1. The nausea and vomiting accompanying pregnancy are due to an allergic reaction of the patient to the secretion of her own corpus luteum of pregnancy.

2. The luteal hormone acting as an allergen is not progesterone but is an unidentified hormone of the corpus luteum.

3. Desensitization may be accomplished by injection of graduated doses of progestin in oil, thus alleviating or stopping the patient's symptoms.

4. Intradermal testing may determine, even before pregnancy, whether a patient will or will not be nauseated when pregnant by determining whether or not she is sensitive to her own secretion.

I wish to express my extreme gratitude for the generous quantities of "proluton," supplied by the Schering Corporation, "lipolutin," supplied by Parke, Davis & Co., "progestin in oil," supplied by Eli Lilly & Co., "progestin in oil," supplied by The Upjohn Co., "progesterone," supplied by G. W. Carnrick Co., and for a quantity of especially prepared progestin in glycerin furnished by The Upjohn Co. Also for specially prepared ampoules of sesame oil, peanut oil, cottonseed oil, and almond oil supplied by these same firms for use in control injections.

I wish to express my appreciation for the great amount of cooperation and assistance given by members of the Obstetrics Staff and the Intern Staff of the University of Oklahoma School of Medicine and University Hospitals.

REFERENCES

- (1) *Finch, J. William*: J. A. M. A. 111: 1368, 1938. (2) *Novak, Emil*: Cyclical Changes in the Ovary, in Curtis Obstetrics & Gynecology, Chapter VIII. (3) *Hirst, B. C.*: A Textbook of Obstetrics, ed. 8, Philadelphia, 1918, W. B. Saunders Company. (4) *Saxon, Leo, and Stoll, John E.*: Illinois M. J. 75: 352, 1939. (5) *Freeman, William, Melick, Joel M., and McClusky, Donald K.*: AM. J. OBST. & GYNEC. 33: 618, 1937. (6) *Kotz, J., and Kaufman, Morton S.*: Ibid. 39: 449, 1940. (7) *Pottenger, F. M., Jr., and Pottenger, F. M.*: California & West. Med. 49: 271, 1938. (8) *Hawkinson, L. F.*: Minnesota Med. 19: 519, 1936. (9) *Hawkinson, L. F.*: J. A. M. A. 111: 1235, 1938. (10) *Brindeau, A., Hinglais, H., and Hinglais, M.*: Compt. rend. Soc. de biol. 124: 349, 1937. (11) *Siebke, Harald*: Zentralbl. f. Gynäk. 53: 2450, 1929. (12) *Costa, N. P., and Cantilo, E.*: Compt. rend. Soc. franc. de gynec. 8: 20, 1938.

OKLAHOMAN BUILDING

Olivella, J. R., and Feo, J. A. R.: Acute Torsion of the Gravid Uterus, Rev. Cubana de obstet. e ginec. 1: 96, 1939.

A 27-year-old woman in the eighth month of her third pregnancy presented the isolated symptom of an intense continuous pain, generalized throughout her abdomen. Palpation and auscultation of the abdomen were difficult, due to spasm of the musculature. A peaklike elevation was noted in the epigastric region. At operation a 90° rotation of a "cordiform" uterus was found. The organ was intensely cyanotic and a greatly distended left cornu apparently caused the elevation noted on inspection of the abdomen. A live fetus was removed through an incision over the anterior aspect of the left cornu.

Hysterectomy is indicated when the viability of the uterus seems endangered, but was not necessary in this case.

R. J. WEISSMAN

Five of those who became pregnant were suffering from true clinical hypothyroidism; the remaining four had unmistakable evidences of subclinical hypothyroidism. No evidence of thyroid dysfunction could be elicited in the group of patients who remained sterile.

Therefore, the effect of thyroid, as an adjuvant or curative measure for sterility, was only demonstrable where a definite lack of thyroid was present. Likewise, where no deficiency in thyroid metabolism existed, the addition of this drug was of no apparent value.

CONCLUSION

Thyroid has a definite and valuable place in the treatment of female sterility only if hypothyroidism is present. It is of little or no value where normal thyroid function exists.

CASE HISTORIES

The following 2 cases are presented in brief, because of their exceptional interest.

CASE 2-A.—Mrs. E. R., aged 27 years, was seen first in November, 1935. Complaint: sterility (6 years) and obesity since onset of puberty. *Past history:* Negative. Husband had gonorrhea ten years previously. *Catamenia:* 12/28-36+/5. Menorrhagia, mild dysmenorrhea. Some clots. No libido. Husband very active sexually.

Physical examination: Height 60 inches; weight 212 pounds; marked generalized obesity. Hirsutes of upper lip, chin, chest and extremities. Pelvic hair distribution resembled male type. Skin was thick, coarse, and dry. Mild pitting edema of face and legs. Thyroid slightly enlarged. Heart and lungs negative. Abdomen negative. Blood pressure 108/80; red blood count 4.1 million; white blood count 7,800; Wassermann negative. Complement fixation for gonorrhea negative.

Pelvic examination: Negative; slight mucoid discharge; smears negative for gonorrhea. Tubal insufflation (December, 1935) showed patency of tubes.

Basal metabolic rate: -28 per cent; *fasting blood cholesterol:* 385 mg./c.c.

Course: In eight months, on a low caloric diet and thyroid to 12 gr. per day, weight was reduced to 173 pounds. In October, 1936, through error, thyroid dosage was doubled without harmful effect. Last menstrual period Jan. 26, 1937. Friedman test positive Feb. 12, 1937.

Prenatal course: Thyroid was slowly decreased to 12 to 14 gr./day after the diagnosis of pregnancy. During the third month, after a particularly violent intercourse, patient began to bleed. Bleeding was controlled with bed rest and morphine. In the seventh month, the patient of her own volition discontinued medication. Two weeks later blood pressure rose to 180/100 mm. Hg. Urinary albumin was present and pitting edema of the extremities was noted. She complained of severe occipital headache, and was immediately hospitalized. Modified Stroganoff therapy plus 20 gr. of thyroid were advised, and ten days later her condition had returned to normal, except for small traces of albumin in the urine. Remainder of prenatal course was negative. Labor, delivery, and post-partum course were normal.

CASE 6-A.—Mrs. R. H., aged 40 years, had an original complaint (June, 1938) of obesity and mild menopausal symptoms. Married fifteen years. No pregnancies. No contraceptives. Libido absent for last five years. *Past history:* negative. Usual childhood diseases. Chronic cholecystitis since 1928.

Menstrual history: 15/28/2-3. Mild cramps. In last year bleeding had decreased both in amount and duration. Occasional hot flushes during the last three months.

Physical examination: Height 62 inches; weight 176 pounds. Moderate obesity of girdle type. Large pendulous breasts. Hair, skin, scalp dry; nails brittle. Some facial hair. Heart and lungs negative; blood pressure 135/80; pulse 66/min. Hg. 80 per cent; basal metabolic rate -14 per cent; fasting blood cholesterol 220 mg./c.c.

body weight depends. Since estrogens are readily secreted in the milk,⁵ the evidence in these animals may not be accepted as conclusive proof of inhibition of lactation. Second, estrogens are known to affect the composition of the milk, increasing the amount of fat and nonfatty solids.⁶ Whether these very immature animals are capable of digesting an altered milk is problematical. Moreover, the mothers were found to have lost considerable weight, indicating an additional systemic response in the maternal organism that was detrimental to her well being.⁷ On the other hand, large amounts of estrogen injected over a period of six days were found to be without effect upon the amount or duration of secretion in the lactating rabbit.⁸ Others have reported a reduction, but not suppression, of lactation with large doses of estrogen in the rat,^{7, 9, 10} goat,¹¹ and cow.^{6, 12}

The hypothesis advanced by Nelson also fails to explain the well-known fact that lactation may continue through successive pregnancies in several species including the rat, rabbit, goat, and the human being. In man especially, increasingly larger amounts of estrogen are produced during pregnancy. In the cow and the rabbit, lactation occurs some twenty and six days, respectively, before parturition.

All in all, the experimental evidence for the inhibition and suppression of lactation by estrogens is far from decisive. The evidence has recently been critically reviewed by Turner.³

In spite of the rather inconclusive experimental data, many clinical reports have appeared, claiming hormonal inhibition and suppression of lactation in the human being. The estrogens (estradiol benzoate, estrone, and lately stilbestrol) have been used in varying dosage.

Sawizki,¹³ using 200 to 800 I.U. of estrone plus 100 R.U. of chorionic gonadotropin, reported successful inhibition of lactation in the human being. Others, finding this dosage far too small, have recommended 30,000 to 50,000 I.B.U. (international benzoate units) of estradiol benzoate as a daily or total dosage over a period of one to five days.¹⁴⁻¹⁷ In a detailed study of the question of dosage, Mayor¹⁸ found that not only was 1,000 I.U. of estrone (0.1 mg.) insufficient, but even 10,000 I.B.U. of estradiol benzoate (1 mg.) administered daily for six to eight days was not enough. Using 250,000 I.B.U. of estradiol benzoate (25 mg.) in oil as a single injection on the first day post partum, he found that of 14 patients so treated, 4 (29 per cent) had no filling, 8 (57 per cent) filled without pain between the fifth and seventh days, while 2 (14 per cent) became fully engorged on the eighth and twelfth days post partum, respectively. Lehman,¹⁹ using a single injection of 100,000 to 150,000 I.B.U. of estradiol benzoate (10 to 15 mg.) the first day postpartum, reported that in a series of 75 cases, 32 per cent had no engorgement, 59 per cent had some secretion or painless filling, while 9 per cent became engorged. For the suppression of established lactation, he found that a single dose of 20 mg. of estradiol benzoate (200,000 I.B.U.) was necessary to yield results in 88 per cent of his series.

The dosage recommended for stilbestrol, the orally active and highly potent synthetic estrogen,* has also been quite variable, ranging from 6 to 80 mg.²⁰⁻²²

Careful analysis of the clinical reports reveals certain inadequacies as a result of which the claims for hormonal inhibition and suppression

*One milligram of stilbestrol is approximately equivalent to 2.5 mg. of estrone or 25,000 I.U. One milligram of estradiol benzoate equals 10,000 I.B.U.

THE EFFECTS OF STILBESTROL UPON LACTATION*

A. R. ABARBANEL, M.D., AND M. J. GOODFRIEND, M.D., F.A.C.S.,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of the Morrisania Hospital)

THE physiologic processes involved in lactation are essentially endocrine in nature. The development of the lobule-alveolar system proceeds under the influence of the ovarian hormones.¹ The initiation of lactation depends upon the anterior lobe of the pituitary, for hypophysectomy during late pregnancy will prevent milk secretion post partum.² The anterior hypophysis also is essential for the maintenance of established lactation, for the removal of the anterior lobe during this time will result in a rapid cessation of milk secretion.² While the initiation of lactation appears to be under purely hormonal influence, the maintenance of established lactation requires a neurogenic factor in addition to the hormonal one. This is the reflex stimulation of the anterior pituitary by the act of suckling for the further secretion of milk. Clearly, then, the process of lactation resolves itself into two fundamental mechanisms: first, the initiation of lactation by hormonal factors, and second, the maintenance of established lactation by both hormonal and neurogenic agencies. The evidence is both experimental and clinical.³

The initiation of lactation post partum has been explained by Nelson in the following manner:¹ The presence of unusually large amounts of estrogen during the latter part of pregnancy inhibits the secretion and action of the lactogenic principle (s) of pituitary. With parturition, the level of the circulating ovarian hormones drops precipitously; the inhibiting influences are thus removed, lactogenic hormone is secreted, and lactation occurs. As experimental proof of this, Nelson offered the following data: Injections of large doses of estrogen into the guinea pig soon after parturition would hold milk secretion in abeyance during the injection period. Lactation, however, would occur within two days after cessation of treatment, or if lactogenic hormone were administered simultaneously with the estrogen. On the other hand, the dosage of estrogen could be so increased that even large doses of the lactogenic hormone would be ineffectual.

Inhibition of lactation by large doses of various estrogens in the experimental animal has been claimed by several workers. Their evidence has been cited as confirming the estrogen inhibition theory. Critical analysis of the results brings to light several serious objections and discrepancies. In the first place, most of the reports dealing with the rat and the mouse showed that a good many of the litters were reared but were stunted in growth. Young rats and mice are particularly sensitive to estrogens, which adversely affect body growth,⁴ upon which, in turn,

*Presented, in part, by Dr. A. R. Abarbanel at the Section on Obstetrics and Gynecology, New York Academy of Medicine, February 27, 1940.

1. In order to observe the effect of stilbestrol upon the initiation of lactation, a group of 25 mothers and babies were chosen in the same manner as the controls. Beginning soon after parturition, varying dosages of stilbestrol, ranging from 50 to 1,000 mg., were administered orally over a course of one to ten days post partum. The babies were allowed to nurse as usual. Briefly summarized, it was found that the onset of lactation on the third or fourth day post partum was not inhibited. It was noted, however, especially when the daily dosage exceeded 15 to 20 mg., that the amount of mother's milk did not reach the average normal range of 8 to 14 ounces daily until two to six days after the stilbestrol had been stopped (Fig. 1). Even with 1,000 mg. (1 Gm.), the secretion of milk was not completely inhibited. In the latter patient, lactation did not become fully established until six days after the last dose of stilbestrol, that is, on the sixteenth day post partum.

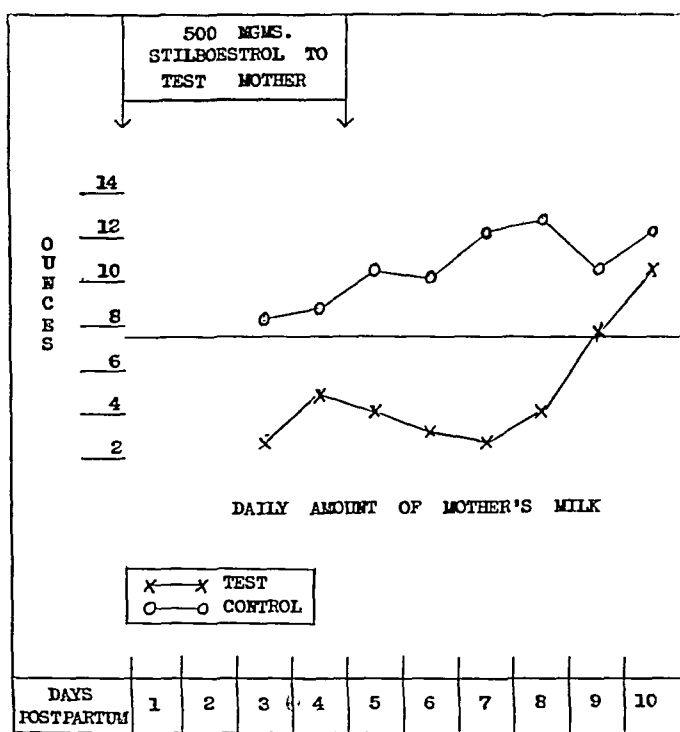


Fig. 1.—The curve of the amount of milk secretion in the control nursing mother compared with that obtained when 500 mg. of stilbestrol was administered orally over the course of four days, beginning soon after parturition. Although the normal onset of lactation was not inhibited, the appearance of the normal average amount of milk secretion was definitely delayed until five days after the last dose of stilbestrol.

From these data, then, it may be said that the estrogen, stilbestrol, will not inhibit the onset of lactation in the nursing human being. It will, however, delay the appearance of the normal average amount of milk secretion. Lactation will be adequately established soon after stilbestrol is discontinued, provided the baby continues to nurse.

2. The effect of stilbestrol upon established lactation in the nursing human being was studied next. Twenty-five mothers were chosen in the same manner as the control group of 50. The babies were allowed to nurse as usual. The test group received varying dosages of stilbestrol ranging from 50 to 500 mg. over a period of two to four days after lactation had been adequately established for twenty-four to seventy-two hours. A minimum of seven and one-half ounces of mother's milk by the fourth day was accepted as normal. In brief, the results obtained demonstrated no apparent suppression of lactation as judged by the baby's daily weight

of lactation in the human being may not be properly evaluated. In the first place, the baby was removed from the breast simultaneously with the administration of the hormone. It is a well-known fact, however, backed up by abundant experimental and clinical evidence, that the maintenance of lactation is dependent upon the nervous stimulus of suckling, or its equivalent.

Furthermore, practically no differentiation seems to have been made between the onset of lactation and painful engorgement of the breasts. These are two distinct phenomena that are not synonymous at all. Painful engorgement is caused by lymphatic and vascular stasis, not by distention of the ducts by milk.²³

Because of the inconclusive experimental and clinical data, the following studies were carried out in order to clarify the effects of estrogens upon lactation in the human being. The estrogen chosen was stilbestrol since it retains most of its potency on oral administration while the latter route requires a minimum of nursing care.

PROCEDURES AND RESULTS

Three hundred and fifteen parturient women were studied. These were divided into several groups. A control group was chosen of 50 apparently healthy mothers who had had normal spontaneous deliveries of normal active babies. Each gave a history of having adequately nursed their previous babies for at least three months. The daily amount of mother's milk was computed from weighing the baby before and after each feeding. The babies were allowed to nurse for twenty minutes five times a day, at four-hour intervals. As the babies did not go to breast at 2 A.M., each received a dilute formula of three ounces at this time.

In this manner, the average normal amount of breast milk obtained by the baby in five daily feedings was found to total from 8 to 14 ounces daily. A daily individual variation was found in practically every patient, ranging from one to as much as six ounces. Interesting, too, is the almost universal drop in the amount of milk obtained on the seventh, eighth, or ninth post-partum day (Fig. 1). At first it was felt that this was due to the fact that the male babies were circumcised on the seventh or eighth day. But as it occurred with female babies, too, the only common denominator that could be discovered was that the mothers were allowed to be up for the first time on either one of these days.

It was found that approximately one-third of the babies were above birth weight, one-third somewhat below birth weight, while the remaining one-third had just about regained their original birth weight by the tenth post-partum day.

Four groups of patients were chosen to answer the following questions:

1. Will the estrogen, stilbestrol, inhibit the onset of lactation in the nursing human being?
2. Will stilbestrol suppress established lactation in the nursing human being?
3. How useful is stilbestrol in preventing or relieving painful engorgement of the breast in the non-nursing mother?
4. Will stilbestrol prevent painful engorgement in the nursing primiparous mother?

pressed for several days. In 31 cases, or 47.7 per cent, the result was termed good. Of these 31 patients mild, transitory heaviness of the breasts was noted on the second to fourth day in 9 cases. In the other 22 patients, some slight fullness or heaviness of the breasts, associated with a transitory watery-chalky secretion in most of them, was noted anywhere from the fifth to the fourteenth day post partum. The only complaint, if any, was a mild transient heaviness or achiness which was adequately relieved with a proper loose uplift breast binder.

In 9 patients, or 13.8 per cent, the results were classified as poor. Analysis of these cases reveals that in 2 of them the pain occurred only in the axillary breast tissue. In another the breasts filled up spontaneously and became painfully engorged on the eighth post-partum day. This patient admitted stripping her nipples because of a slight watery secretion. In 3 others, it was observed that the breast binder had been made so tight that when filling occurred, it went on to painful engorgement of the breasts associated with lumpiness at the region where the binder had cut across the breast. Simple adjustment of the binder frequently gave marked relief.

It is interesting to observe that one of these patients expressed a desire to nurse her baby on the eighth post-partum day. Her breasts, which had remained soft and asymptomatic, were pumped four times and a total of 2 ounces were secured in twenty-four hours. In seventy-two hours, however, her baby was receiving 12 ounces daily from the breast. On the basis of this case, a small series of patients have been treated in the following manner: If, at delivery, an indication is present for the mother not to nurse for the first few days post partum, such as an upper respiratory infection, the mother receives 15 mg. of stilbestrol daily for three to six days. The baby is permitted to suckle when the mother is again well. Lactation soon becomes adequate.

In the control group of 65 patients who did not receive hormonal therapy, severe painful engorgement of the breasts occurred in 31, or 47.7 per cent. Mild engorgement, enough to make the patient complain of fullness or heaviness with occasional secretion of milk, was noted in 29 cases, or 44.6 per cent. Here again a loose uplift breast binder was usually sufficient to give adequate relief. In 5 cases, or 7.7 per cent, the patient remained symptomless.

Analysis of these data reveals that about 50 per cent of the control group complained of painfully engorged breasts. With stilbestrol therapy, only 13.8 per cent, or 1 in 7, suffered. In short, the use of stilbestrol had prevented painful engorgement in more than 70 per cent of the patients that would have suffered from it.

There were 35 patients in whom established lactation had to be interrupted for various indications. Stilbestrol was only administered to those patients who had been lactating well up to the time interruption was deemed necessary. If a patient, for example, had fissured nipples because the baby had been suckling mightily on a poorly lactating breast, she was not given hormonal therapy unless actual painful engorgement occurred. Fluids were administered freely; in fact, in many cases they were actually forced. Each received a loose uplift breast binder.

Since most of these patients would have been relieved in two or three days on symptomatic therapy, our criterion of a successful result necessarily had to be a strict one. Accordingly, only if practically complete relief was secured within twenty-four hours, was the therapeutic result deemed successful.

The following schedule of dosage was evolved after several preliminary trials. On instituting therapy, 25 mg. of stilbestrol were given at once. The next day two doses of 5 mg. each were followed by 5 mg. daily for three days. Total dosage, therefore, was 50 mg.

Of this group of 35, the results in 30, or 85.7 per cent, were considered as successful. Of the 5 failures, 2 can be ascribed to inadequate dosage. Although the breasts continued to feel lumpy for one or two more days, no pain was noted. In many, secretion was still present anywhere from two days to three weeks later. In 6, a late secondary, slight, painless filling of the breasts, transitory in character, was recorded.

Consequently, when all these results are carefully reviewed, it is found that stilbestrol is, indeed, a rather useful therapeutic agent both in preventing and relieving painful engorgement of the breasts in the non-nursing mother.

as well as the amount of milk secretion daily (Fig. 2). Careful pediatric check-up and follow-up revealed no apparent side effects upon the babies.

Clearly, then, the estrogen, stilbestrol, in dosages ranging up to 500 mg. does not affect established lactation in the nursing human being.

3. The efficacy of stilbestrol in preventing or relieving painful engorgement in the non-nursing mother was then determined. One hundred and sixty-five patients formed the basis for this study. For various indications, 100 of these women either did not nurse their babies or else established lactation had to be interrupted. Accordingly, two groups of patients were treated. There were 65 cases in the group where the indication for not nursing was present at the time of delivery. A similar group of 65 patients who were not treated served as controls. (Postabortal cases were not included in this series, since it was found that in the vast majority the degree of painful engorgement was very mild, if it occurred at all, and the amount of lactation, if any, quite slight and transitory.)

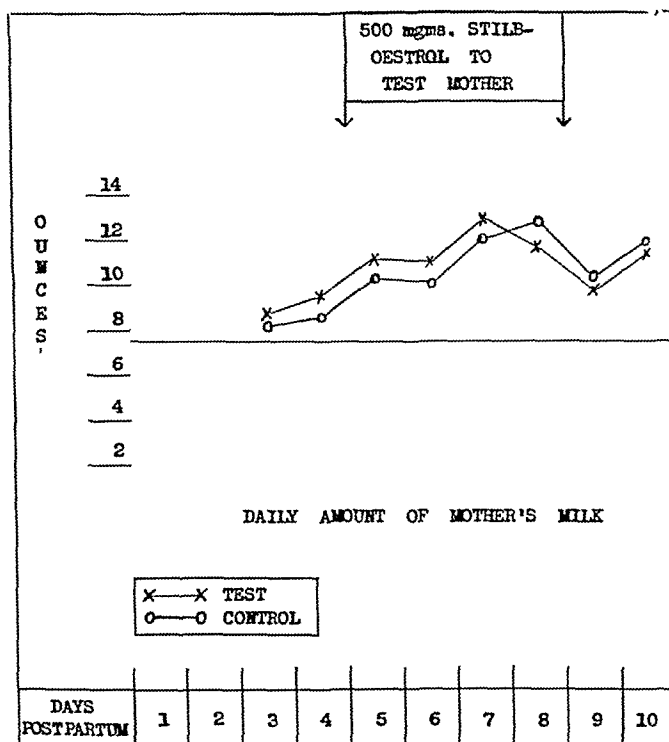


Fig. 2.—Failure of 500 mg. of stilbestrol to affect established lactation in the nursing human being.

After preliminary trials with varying dosages ranging from 10 to 100 mg. over two to ten days, it was found that the most consistent results were obtained with the following schedule. Five milligrams of stilbestrol were given twice the day of delivery and then once a day for three or four days. In multiparas, who gave a history of having lactated well before, the same dosage was continued for five or six days. The total dosage, therefore, ranged from 25 to 40 mg. Fluids were administered freely; in some, they were actually forced. A loose, not tight, uplift binder was used where indicated.

Results were tabulated as excellent if no engorgement occurred, either early or late. The result was classified as good if some mild transitory heaviness or slight filling up of the breasts occurred which could be readily relieved merely by using an adequate loose uplift breast binder. The outcome was termed poor if any painful engorgement occurred.

Of these 65 cases, there were 25 patients, or 38.5 per cent, in whom the result could be termed excellent even though in 14 some secretion could be readily ex-

pituitary.²⁵ The former premise seems to be the correct one, for Reece,²⁶ using colchicine, has shown that injections of estrogen in the rat would bring about an extensive proliferation of the glandular cells of the breasts, as shown by the increased mitotic count. Since a cell that is proliferating cannot very well secrete at the same time, it is assumed that the action of estrogens is a direct one upon the glandular epithelium. Folley and Kon⁷ had a similar idea, when they stated that the ability of a substance to inhibit lactation seemed to parallel the proliferating effect of that substance upon the mammary glands.

The hypothesis outlined above seems to explain the effect of large doses of stilbestrol upon the onset of lactation in the nursing human being. The proliferating effect of stilbestrol upon the mammary gland is the same as that of estrone.²⁷ The apparent cause for the reduced amount of milk secretion during administration of this estrogen becomes discernible (Fig. 1). Since estrogens raise the lactogenic content of the pituitary, whose release seems to be stimulated by the act of suckling,²⁸ it now becomes clear why, soon after the administration of estrogen is stopped, the amount of milk secretion rapidly becomes normal in the nursing human being.*

The maintenance of lactation involves both hormonal and neurogenic factors. It is a well-known clinical and experimental fact that the secretion of milk will soon cease if suckling, or its equivalent, is stopped. Once lactation is adequately established, relatively massive doses of stilbestrol proved quite ineffectual in suppressing milk secretion in the nursing human being (Fig. 2). Similar negative results have been obtained with 500 mg. of testosterone propionate, 550 mg. of methyl testosterone, 100 mg. of progesterone and 500 mg. of pregnenolone.²⁴

The exact mechanism by which the nervous stimulation of nursing maintains lactation is still not clear on the basis of our present knowledge.³ Suckling appears to be a powerful reflex stimulus for the release of lactogenic hormone from the pituitary, thus maintaining lactation.²⁸ The centrifugal arm of this reflex directly involves the nerves leading to the spinal cord, for denervation of all the exposed breasts by a spinal cord lesion leads to rapid cessation of milk secretion even if the young continue to nurse.²⁹ The centripetal arm of this reflex is hormonal, for denervated or transplanted mammary glands will continue to lactate provided a normal breast of that animal is stimulated to secrete by suckling.³⁰

The act of nursing, then, seems to be a much more powerful stimulus for the secretion of milk by the glandular epithelium of the breast than 500 mg. of stilbestrol is a stimulus for proliferation of this same epithelium. This explains why established lactation may be maintained in several species, including man, through successive pregnancies.

*Recently, Folley, Watson and Bottomley (J. Physiol. 98: 15, 1940) reported that they were able to stimulate the appearance of lactation in 2 virgin goats by combining local application of stilbestrol with mechanical massage of the mammary gland. Somewhat similar observations were noted in these studies in a patient whose breasts had never filled, much less lactated, after four previous full-term pregnancies. She received 50 mg. of stilbestrol during the first two post-partum days. The baby was put to breast. On the fourth day, her breasts became engorged for the first time in her life. Milk secretion soon appeared, but proved to be inadequate, totalling 2 to 3 ounces daily. This evidence, however, is only suggestive, being far from conclusive.

4. The usefulness of stilbestrol in preventing painful engorgement in the nursing primiparous mother was then determined, since painful engorgement of the breasts is especially common in this group. Accordingly, 50 primiparas were divided into two groups of 25 each. The test group received 5 mg. of stilbestrol daily for the first three days post partum. In the control group there were 10, or 40 per cent, who suffered from painful engorgement for twenty-four to forty-eight hours, another ten, or 40 per cent, who complained of mild to moderate heaviness, achiness, or tightness of the breasts, while only 5, or 20 per cent, were practically symptom free. In the test group, there were only 2, or 8 per cent, who complained of heaviness and achiness, 2, or 8 per cent, who stated they felt some tightness, and 21, or 84 per cent, whose breasts filled painlessly. The onset of normal lactation was not affected at all.

From these results it is readily seen that stilbestrol is very effective in preventing painful engorgement of the breasts in the nursing primiparous mother, while not interfering noticeably with lactation.

DISCUSSION

Adequate comprehension of the fundamental endocrine physiology of the secretion of milk by the mammary gland necessitates a clear differentiation of the phenomena of the initiation of lactation, the maintenance of established lactation, and the clinical syndrome of painful engorgement of the breasts. Only when this is done may the many seemingly contradictory reports, experimental and clinical, be interpreted correctly.

The initiation of lactation appears to be, basically, hormonal in nature, involving formative stimuli from the ovarian hormones and functional stimuli by lactogenic principles of the anterior lobe of the pituitary. The role played by other endocrine glands, especially the thyroid and adrenal, appears to be secondary, involving water balance as well as nutritional and metabolic factors. It is conceivable, then, that the onset of lactation in the human being might be inhibited by preventing the change in hormonal balance that occurs with parturition. The only substance which yielded any suggestive results was the estrogen stilbestrol.

Although the actual onset of lactation at the usual time was not inhibited by stilbestrol, the appearance of the average normal amount of milk secretion was materially delayed when large doses were given soon after delivery (Fig. 1). Reece and Turner reported similar results with estrogens in the rat.¹⁰ That the onset of lactation might have been completely inhibited if a still larger dosage of stilbestrol had been administered soon after parturition must be considered. On the other hand, similar experiments using 250 mg. of testosterone propionate, 500 mg. of methyl testosterone, 100 mg. of progesterone, and 500 mg. of pregnenolone failed to demonstrate any delay in the appearance of the onset of the average normal amount of milk secretion in the nursing human being.²⁴

Most reports have postulated that estrogens inhibit the production of the lactogenic principle(s) of the anterior pituitary and thus inhibit lactation. Turner,³ however, feels that inhibition of lactation, when it occurs, involves either a direct action upon the epithelium of the mammary gland, or possibly an inhibition of the release of lactogenic hormone from the pituitary, for his group found that treatment with estrogens would markedly raise the lactogenic content of the rat's

SUMMARY

The synthetic estrogen, stilbestrol, when administered orally soon after parturition in dosages up to 1,000 mg. did not inhibit the actual onset of lactation in the nursing human being. The appearance of the average normal amount of milk secretion, however, was delayed until as many as five or six days after the last dose of stilbestrol.

No effect at all was noted upon established lactation in the nursing human being with 50 to 500 mg. of stilbestrol administered orally in divided doses over a period of one to four days.

In the prevention of painful engorgement of the breast in 65 non-nursing full-term mothers, 25 to 40 mg. of stilbestrol orally in divided doses failed to yield a satisfactory result in but 9, or 13.8 per cent. On the other hand, in a control group of 65 similar cases, 31, or 47.7 per cent, suffered from painful engorgement of the breasts.

In 35 cases where adequate established lactation had to be interrupted, 50 mg. of stilbestrol orally in divided doses provided satisfactory relief for painful engorgement within twenty-four hours in 30, or 85.7 per cent.

Of 25 primiparous nursing mothers given 5 mg. of stilbestrol daily for the first three post-partum days, practically painless and asymptomatic filling of the breasts occurred in 21, or 84 per cent. In the control group, however, only 5, or 20 per cent, had painless filling of the breasts.

The pregnant and puerperal patient was found to be unusually tolerant of huge doses of stilbestrol.

The authors gratefully acknowledge the sincere interest of Dr. Harry Aranow during the course of these studies. In addition, the splendid cooperation of the Misses Andes, White, and Mills of the nursing staff of the Obstetrical Division was deeply appreciated.

The stilbestrol used in this study was kindly supplied by Dr. J. A. Morrell of E. R. Squibb & Sons.

REFERENCES

- (1) *Nelson, W. O.*: *Physiol. Rev.* 16: 488, 1936. (2) *Selye, H.*: *Am. J. Physiol.* 107: 535, 1934. (3) *Turner, C. W.*: *Sex and Internal Secretions*, ed. 2, Baltimore, 1939, Williams and Wilkins, Chap. XI. (4) *Gardner, W. U., and Pfeiffer, C. A.*: *Proc. Soc. Exper. Biol. & Med.* 37: 678, 1938. (5) *Hain, A. M.*: *Quart. J. Exper. Physiol.* 25: 131, 1935. (6) *Folley, S. J., and Watson, H. M. S.*: *Lancet* 2: 423, 1938. (7) *Folley, S. J., and Kon, S. K.*: *Proc. Roy. Soc., Lond., ser. B*, 124: 476, 1938. (8) *Smith, G. V. S., and Smith, O. W.*: *Am. J. Physiol.* 103: 356, 1933. (9) *Anselmino, K. J., and Hoffman, F.*: *Zentralbl. f. Gynäk.* 60: 501, 1936. (10) *Reece, R. P., and Turner, C. W.*: *Proc. Soc. Exper. Biol. & Med.* 36: 283, 1937. (11) *Fremery, P. de J.*: *J. Physiol.* 87: 10, 1936. (12) *Waterman, L., Freud, J., and de Jongh, N.*: *Acta. brev. Neerland.* 6: 1, 1936. (13) *Sawizki, W.*: *Zentralbl. f. Gynäk.* 59: 2784, 1935. (14) *Ramos, A. P., and Colombo, E.*: *Deutsche med. Wchnschr.* 64: 782, 1938. (15) *Gavioli, R. L.*: *Semana méd.* 2: 130, 1938. (16) *Bottiroli, E.*: *Ibid.* 1: 688, 1939. (17) *Adrian, J.*: *Gynec. et obst.* 37: 178, 1938. (18) *Mayor, J. M.*: *Zentralbl. f. Gynäk.* 60: 2379, 1936. (19) *Lehman, G.*: *München. med. Wchnschr.* 85: 1781, 1938. (20) *Limber, H.*: *Zentralbl. f. Gynäk.* 63: 1910, 1939. (21) *Varagnot*: *Bull. Soc. Gynec. et Obst.* 28: 426, 1939. (22) *Kellar, R. J., and Sutherland, J. K.*: *J. Obst. & Gynaec. Brit. Emp.* 46: 1, 1939. (23) *Beck, A. C.*: *Obstetrical Practise*, Baltimore, 1935, Williams and Wilkins, Chap. XVI. (24) *Abarbanel, A. R.*: Unpublished data. (25) *Reece, R. P., and Turner, C. W.*: *Proc. Soc. Exper. Biol. & Med.* 34: 402, 1936. (26) *Reece, R. P., Bartlett, J. W., Hathaway, I. L., and Davis, H. P.*: *Proc. Soc. Exper. Biol. & Med.* 43: 186, 1940. (27) *Jacobsen, E., and Christensen, S. S.*: *Acta. path. et microbiol. Scandinav.* 16: 359, 1939. (28) *Reece, R. P., and Turner, C. W.*: *Proc. Soc. Exper. Biol. & Med.* 35: 621, 1937. (29) *Ingelbrecht, P.*: *Compt. rend. Soc. de Biol.* 120: 1369, 1935. (30) *Stricker, P.*: *Compt. rend. Soc. de Biol.* 102: 1076, 1930. (31) *Abarbanel, A. R.*: *AM. J. OBST. & GYNEC.* 38: 1043, 1939. (32) *Shorr, E., Robinson, F. H., and Papanicolaou, G. N.*: *J. A. M. A.* 113: 2312, 1939.

Painful engorgement of the breast is caused by lymphatic and venous stasis, not by distention of the ducts with milk.²³ Unfortunately, most of the clinical reports on the effect of estrogens upon lactation in the human being have confused painful engorgement with the onset of lactation, using these terms interchangeably. These are two distinct and separate phenomena. By what means painful engorgement is prevented or relieved by the various sexual hormones cannot be explained on our present-day knowledge. That it is not by inhibition of lactation is obvious from the fact that lactation may proceed normally as in the nursing primiparous mothers treated with stilbestrol. A similar finding has been reported with testosterone propionate.³¹

The delayed filling of the breasts and secretion therefrom that was noted in some of the non-nursing group may be explained in the following manner: The administration of estrogen brought about an increased lactogen content of the pituitary. After the stilbestrol was stopped, the lactogenic hormone was now free to act upon a breast already suitably prepared by the previous pregnancy.

An illustrative case is that of the mother who received stilbestrol after the baby was removed from the breast because of fissured nipples. Six days later her breasts began to fill up again. A second course of stilbestrol was given. Seven days later her breasts again filled up and ran over with milklike secretion.

The results obtained with stilbestrol orally in preventing painful engorgement of the breasts in the nonnursing mother are quite similar to those reported with 10 to 25 mg. of estradiol benzoate given intramuscularly in oil.^{18, 19} With stilbestrol, the result was termed excellent in 38.5 per cent as compared to 29 per cent¹⁸ and 32 per cent¹⁹ when estradiol benzoate was used. With the latter estrogen failures occurred in 14 per cent¹⁸ and 9 per cent,¹⁹ while with stilbestrol 13.8 per cent failed to respond. The advantages, then, lie with stilbestrol for two reasons: First, it is active orally, requiring a minimum of nursing care. Second, the cost of stilbestrol is extremely little compared to that of the natural estrogen. The only disadvantage of the estrogens, it seems, is the late secondary filling that so frequently occurs. This may be obviated to a great extent by using an adequate uplift breast binder that is *loose*, not tight. A second course of stilbestrol is rarely, if ever, necessary.

COMMENT

Stilbestrol has been reported to have so-called "toxic" effects in the nonpregnant individual.³² Two puerperal patients were given 1500 mg. (1.5 Gm.) during the course of ten and twelve days, respectively. Complete blood chemistries, urine examinations, blood counts, etc., before, during, and after the administration of this enormous dose failed to reveal any "toxic" effects. One patient felt slightly dizzy for about thirty minutes after a dose of 50 mg. Pre-eclamptic and eclamptic patients with uric acid values between 7 and 9 were given as much as 150 mg. of stilbestrol in the space of twenty-four hours for inducing labor with no untoward effects. Presumably the pregnant and puerperal patient can metabolize stilbestrol more efficiently than the nonpregnant one.

Pelvic examination: Vaginal mucous membranes pale. Cervix, uterus, and adnexa negative. Tubal insufflation not done.

Course: Thyroid gradually increased to 4 gr. per day. Basal metabolic rate +18 per cent. Weight loss averaged 2 pounds a week. Last menstrual period Sept. 10, 1938; Friedman test positive on Oct. 30, 1938. Because of advancing age she did not wish for a child, and so, against advice, underwent an induced abortion.

REFERENCES

- (1) *Marine, D.*: *Physiol. Rev.* 2: 536, 1922. (2) *Achneur*: *Die Blutdrüsen-erkrankungen des Weibes*, Wiesbaden, 1918. (3) *Litzenberg, J. C.*: *AM. J. OBST. & GYNEC.* 12: 706, 1926; *Litzenberg, J. C., and Carey, J. B.*: *Ibid.* 17: 550, 1929. (4) *Rowe, A. W.*: *J. A. M. A.* 95: 1219, 1930. (5) *Berkman, J. M.*: *Ibid.* 106: 2042, 1936. (6) *Hutchens, H. T.*: *AM. J. OBST. & GYNEC.* 12: 764, 1926. (7) *Maser, C., Isreal, S. L., and Charney, C. W.*: *Pennsylvania M. J.* 40: 1009, 1938. (8) *Kurzrock, R.*: *Endocrines in Obstetrics and Gynecology*, p. 426, 1937. (9) *Rubin, I. C.*: *J. A. M. A.* 90: 99, 1928; *AM. J. OBST. & GYNEC.* 24: 561, 1932. (10) *Baer, J. L.*: *AM. J. OBST. & GYNEC.* 2: 49, 1921. (11) *Cornell, E. L.*: *Surg. Gynec. Obst.* 36: 53, 1923. (12) *King, E. L., and Herring, J. S.*: *J. A. M. A.* 113: 1300, 1939. (13) *Foster, N. B.*: *Nelson's Loose Leaf Medicine* 3: 292, 1938. (14) *Nicholson*: *J. Obst. & Gynaec. Brit. Emp.* 5: 32, 1904. (15) *Stander, J. H., and Peckham, C. H.*: *Bull. Johns Hopkins Hosp.* 38: 227, 1926. (16) *Vorzimer, J., Fishberg, A. M., Langrock, E. G., and Rappaport, E. M.*: *AM. J. OBST. & GYNEC.* 33: 801, 1937. (17) *Laurence, C. H., and Rowe, A. W.*: *Endocrinology* 12: 337, 1928. (18) *Murrey, G. R.*: *Practitioner* 140: 1, 1938. (19) *Campbell, A. D.*: *Surg. Gynec. Obst.* 68: 489, 1939. (20) *vanTongeren, F. C.*: *Gynéc. et obst.* 33: 239, 1936.

935 PARK AVENUE

A METHOD FOR RECORDING AND REPRODUCING FETAL HEART SOUNDS

ARTHUR L. SMITH, A.M., M.D., F.A.C.P., LINCOLN, NEB., AND
W. J. HERVERT, A.B., B.Sc., M.D., VALPARAISO, NEB.

MANY statements concerning fetal heart sounds have been copied and recopied until they have actually become medical folklore. But since none of these are based upon accurate methods of measurement, we decided it might be worth while to see how much truth and how much fiction there is in these conclusions. Some of these are:

1. The fetal heart rhythm is the ticktack type, that is, systole and diastole are of the same duration.
2. The condition of the fetus can be judged by its heart rate. (Plass¹ does not agree with this.)
3. The first sound is always the accented one.
4. The maternal and fetal hearts vary directly in rate.

One of us (W. J. H.) examined and delivered the patients reported and the other (A. L. S.) did the graphic and auditory recordings of the maternal and fetal heart sounds.

REVIEW OF LITERATURE

The review of the literature reveals few successful attempts to record fetal heart sounds.

Strassman and Mussey²⁻⁴ described a method of taking electrocardiograms of fetal hearts and the resulting small waves show in the maternal electrocardiogram.

PROLAPSE AND TORSION OF THE RIGHT FALLOPIAN TUBE WITH VAGINAL BLEEDING, FOLLOWING VAGINAL HYSTERECTOMY

JOHN O. BOWER, M.D., F.A.C.S., A. E. PEARCE, M.D., AND
E. W. CONWAY, M.D., PHILADELPHIA, PA.

(From the Service of the St. Luke's and Children's Hospitals)

THE following case presents an unusual complication following vaginal hysterectomy: prolapse of the fimbriated extremity of the right Fallopian tube through the drainage site at the apex of the vaginal vault, torsion of the tube, and intermittent bleeding from the fimbriated ostium.

Mrs. A. M. W., aged 25 years, housewife, was seen by one of us for the first time on Aug. 20, 1939. She had had periumbilical pain and profuse diarrhea for two days. Both responded to paregoric and her symptoms subsided completely in twenty-four hours. She was asked to return for more thorough study because of the following history:

Her menses had begun at 14 years of age, occurring irregularly every two to three weeks, lasting six to nine days, with severe hypogastric cramps beginning one week before and continuing through the entire period. Previous operations were a tonsillectomy at eight years of age and an appendectomy with drainage at the age of seventeen. She was married late in 1935 and had one child in June, 1936.

She was hospitalized on Jan. 31, 1938, complaining of pain in the left inguinal region before and during periods and the passage of clots at the menses with relief. Her pain was very severe for eleven months before admission. The period occurring from Jan. 25 to 30, 1938, was the shortest of her experience.

Physical examination revealed markedly carious teeth and a few apical râles bilaterally; pelvic examination demonstrated a small introitus, good perineal support, normal vagina, small cervical scar, first degree prolapse of the uterus with marked retroversion and a fullness in the left adnexal region. Urinalysis, negative; hemoglobin, 85 per cent; erythrocytes, 4.4; leucocytes, 9,000; differential, normal; sedimentation rate, normal.

A diagnosis of obstructive dysmenorrhea and ovarian menorrhagia was made and on Feb. 2, 1938, under gas-ether anesthesia, a dilatation and curettage and right oophorectomy were performed. The right ovary was cystic, but the left adnexa and uterus were normal. No pathologic diagnosis of the endometrium was made. She was discharged Feb. 13, 1938, with a slightly elevated temperature, 99° F.

Readmissions.—On April 4 to April 11, 1938, she re-entered the hospital complaining of frequent menses and menorrhagia. She had menstruated from February 19 to 27 with less pain than preoperatively; from March 2 to 11, 1938, and from March 24 to April 2, 1938. Left inguinal tenderness was present. Urine, blood count, and sedimentation rate were normal. Temperature was 99.2° F.

From May 16 to May 22, 1938, she again was hospitalized, complaining of periumbilical cramps, bleeding every thirteen days for seven days, and dysmenorrhea. Urine and sedimentation rate were normal; hemoglobin, 75 per cent; erythrocytes, 4.1; temperature was normal except for two days when it was over 99° F.

On Aug. 15 to Sept. 2, 1938, she complained of menorrhagia and metrorrhagia. An x-ray of the chest showed inactive apical tuberculosis; basal metabolic rate, plus 4; Wassermann and Kahn reactions, negative; hemoglobin, 76 per cent. On Aug. 16, 1938, a vaginal hysterectomy was performed; a cigarette drain was removed in forty-eight hours. Pathologic report stated that the uterus had atrophic mucosa, an

eroded cervix and corporal fibrosis. When discharged, her temperature was normal, and there was no bleeding.

In October, 1938, she bled slightly, and in November severe bleeding occurred. This was repeated at least bimonthly for one to six days, and was associated with pain in the lower left abdomen. She was given various forms of hormone and snake venom therapy with no relief.

Her last bleeding seemed to occur suddenly and lasted from Aug. 21 to Aug. 23, 1939. On Aug. 24, 1939, physical examination revealed a loss of 35 pounds in weight. At the apex of the vaginal vault we found a small nodular mass about 1 cm. in diameter which appeared edematous and seemed to be covered with small papillary projections (Fig. 1). A diagnosis of endometrioma of the vaginal vault was made. She was re-examined on Aug. 26, 1939, by one of us who thought the vaginal mass was a polyp. (At the time we were under the impression that her tubes had been removed as well as the uterus.)

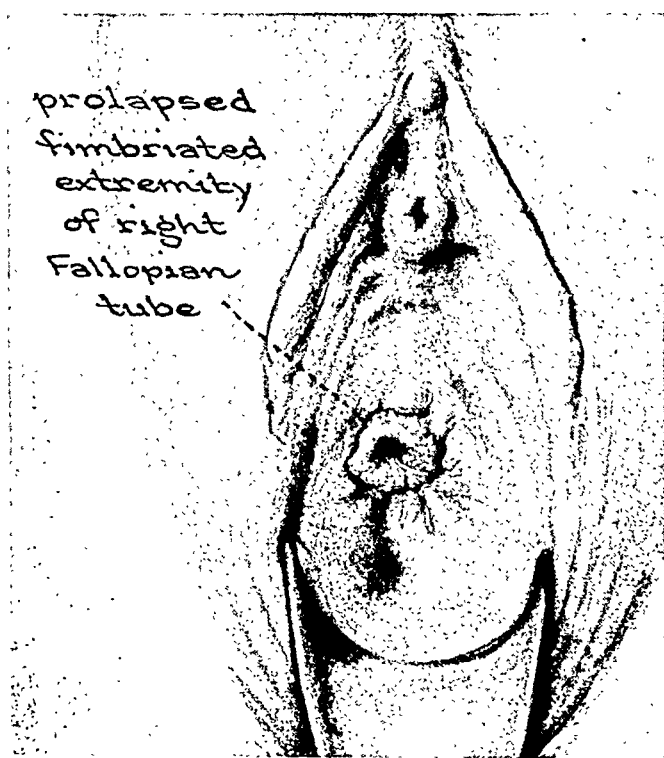


Fig. 1.—Mass covered with papillary projections at apex of the vaginal vault.

She entered the hospital on Aug. 27, 1939 (hemoglobin, 90 per cent; erythrocytes, 4,55; leucocytes, 4,800; differential, normal), and was operated upon the following day. Through the vagina, a portion of the mass was grasped with a tenaculum. The operator was unable to loosen it, so a piece was excised for tissue study.

Because of the possibility of a prolapsed tube, the abdomen was opened through a midline infraumbilical incision. The left ovary was cystic and badly degenerated. A cyst of Morgagni was present on the right side. The fimbriated end of the right tube was found to disappear into the vaginal vault; it was pulled up and a bilateral salpingectomy and right oophorectomy were done (Fig. 2). The two leaves of the broad ligament were drawn together over the opening in the vaginal dome. The abdomen was closed in layers without drainage. Convalescence was uneventful, and she was discharged on Sept. 5, 1939.

Pathologic Report.—Left ovary was 3 cm. in diameter, and there were multiple cysts with degeneration. Both tubes were degenerated. The right tube contained

a cyst of Morgagni 1 cm. in diameter. The right tube was edematous and the villi hypertrophied; there was extreme congestion and edema of the walls of the blood vessels with old and new thrombi and cellular infiltration. The stroma contained areas of hyalinization. There was no evidence of ectopic endometrium (Fig. 3).

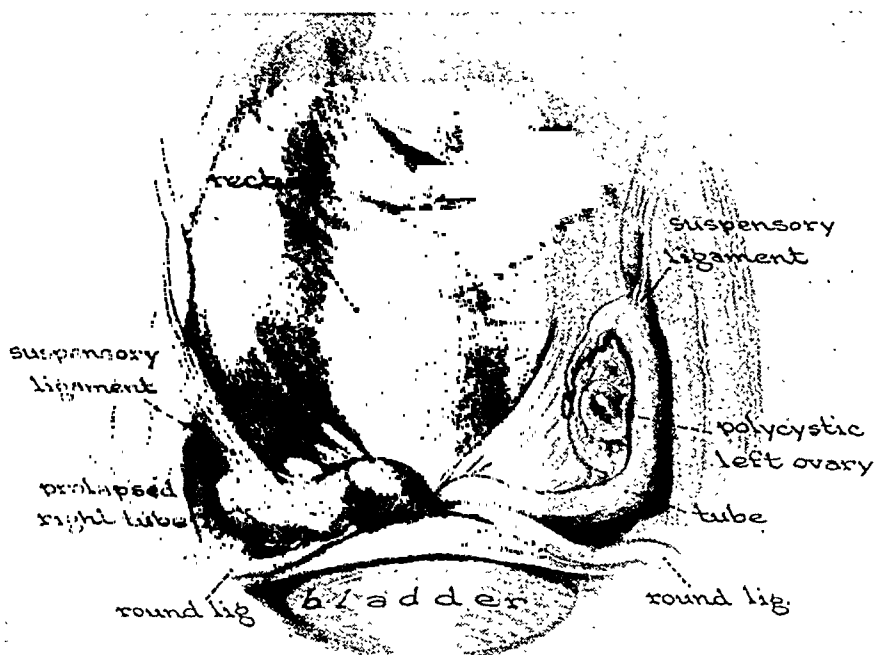


Fig. 2.—Visualization of fimbriated end of right tube disappearing into vaginal vault. Right ovary had been removed previously. Left ovary cystic and badly degenerated.

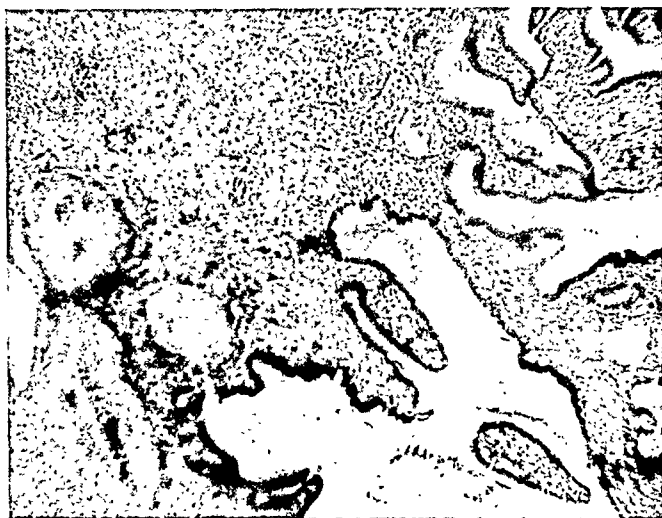


Fig. 3.—Microscopic section ($\times 80$) of right Fallopian tube showing hypertrophy of villi, congestion, edema of the walls of the blood vessels with old and new thrombi and cellular infiltration. The supporting stroma contains areas of hyalinization.

Diagnosis.—Torsion of Fallopian tube.

At patient's last visit (Oct. 22, 1940), she stated that there was neither bleeding nor vaginal discharge. She had gained 27 pounds. Flushes were controlled effectively by the use of estrogenic hormones.

COMMENT

It is reasonable to assume that the cigarette drain, which was removed forty-eight hours after the vaginal hysterectomy, offered the hiatus through which the fimbriated extremity of the right Fallopian tube prolapsed. It is also possible that the fimbriae might have become adherent to the gauze of the drain and been inadvertently pulled through the hiatus when the drain was removed. Torsion of the structure then occurred with resultant edema, venous congestion and hemorrhage. Whether or not endocrine imbalance added to this mechanical derangement with resultant periodicity of bleeding, we are unable to say.

COBRA VENOM FOR INTRACTABLE PAIN

JOSEPH W. KELSO, M.D., OKLAHOMA CITY, OKLA.

(From the Gynecological Service of the University Hospital)

BECAUSE of the long-continued intractable pain associated with incurable pelvic cancer, and the disappointing results of the anodyne measures usually employed, morphine addiction, nausea, vomiting, insomnia, and euphoria so frequently seen making the use of these analgesic measures unsatisfactory, the author decided to try cobra venom for the relief of pain.

Cobra venom was studied by Dr. Adolph Monae-Lesser in 1929. He observed the relief of pain in a Cuban leper who was bitten by a tropical spider. This experience caused him to study the action of cobra venom. Dr. David I. Macht deserves the credit for a greater part of the physiologic and pharmacologic data which have been obtained from work done in the United States. He has proved conclusively that the venom, like morphine, has its effect on the higher centers of the brain and has no peripheral action at all. Dr. Macht has likewise carried on a biochemical investigation in which he has established the fact that opium derivatives are oxidized from the brain very rapidly, while the venom from the cobra is found unchanged in fresh brain tissue for a much longer period of time. This explains its tardy action and its prolonged anodyne effect in contradistinction to morphine. The latter produces rapid analgesia, but unfortunately the effect is not very lasting. Fortunately cobra venom is not habit forming. In other words, a patient is not likely to become addicted to a drug from which he obtains no relief for seventy-two hours after administration.

On the basis of experimental clinical observations made by Dr. Macht and others, I have used this drug on 18 patients, 15 of whom were considered hopeless.

CASE REPORTS

A. T., 57 years of age, had a Group IV carcinoma of the cervix and received 7,200 r. units of x-ray. After temporary improvement she developed pain and continued bleeding. Cobra venom was started in August, 1939, by Dr. C. W. Ohl, of Chickasha, Oklahoma. Her malignancy advanced and she continued to bleed on repeated occasions, but in spite of this she has gained weight and has been relieved of pain. This patient continued to be comfortable on 5 mouse units, or 1 c.c. of the cobra venom every third day.

T. L. W., 50 years of age, Group III cervical cancer, received x-ray and radium, but after eight months the growth began to progress rapidly and she developed unbearable pain. Cobra venom was begun in August, 1939, under the supervision

of Dr. C. M. Cochran, Okemah, Oklahoma. Though quantities of anodyne pills had been given, she experienced little relief from pain until cobra venom was administered. The control of pain was almost 100 per cent. Although she continued to lose weight, she gained in strength and well-being.

O. D., 65 years of age, Group III carcinoma of the cervix, had a pathologic fracture through the neck of the left femur and has obtained 100 per cent relief from her pain since the use of the venom, which has been given by Dr. L. R. Wilhite, of Perkins, Oklahoma. Her fracture has united, there is no evidence of bone destruction, and at the present time she takes 5 units weekly and is without pain.

N. J., 40 years of age, had a Group III carcinoma of the cervix, received radium and x-ray, but a year later began to have severe pain. She was given cobra venom by Dr. D. B. Collins, of Waurika, Oklahoma. He thought she was obtaining relief from the injections, but later learned that she was taking papine for control of pain. It is interesting to note that she did eat well and gained weight after the venom was started, whereas she had lost fourteen pounds in the previous two months. The patient died of a pulmonary embolus. She is reported here as obtaining no relief from the use of the venom.

E. N., 44 years of age, Group III cervical malignancy, was bedfast because of pain, anorexia, nausea, and vomiting from the use of aspirin. After two months' routine administration of cobra venom she gained weight and reported 85 per cent relief from pain. She found it unnecessary to continue its use, but after eight weeks she again began its administration and obtained satisfactory relief on an ampoule every third day.

M. B., 53 years of age, Group II cervical malignancy, had an extension into the vesicovaginal area which caused severe pain. Cobra venom given by Drs. Cotton and Van Matier, of Walters, Oklahoma, afforded complete relief after the sixth injection. The attending physicians confirm the above report and state that all opiates were discontinued, and after two months have found it unnecessary to continue with the drug.

L. N., 39 years of age, had a cervical stump malignancy, Group IV, with metastasis into the bladder. After six daily injections of cobra venom, she was just as comfortable on $\frac{1}{8}$ gr. of morphine sulfate as she had been on $\frac{1}{4}$ gr. She was difficult to control and insisted upon leaving the hospital. Since it was impossible to evaluate results, she is reported as receiving no relief.

I. M. O., 32-year-old negro woman, carcinoma of the cervix, Group III, received the maximum amount of x-ray and radium. In spite of this, she was losing weight at the rate of 7 pounds a week because of constant, severe pain in her pelvis. After three injections of the venom she became comfortable, although the pain had previously required large doses of morphine. Her injections have been gradually reduced in frequency, and she is now receiving 5 units every sixth day, remaining absolutely free of pain. There is a weight gain of 35 pounds. During the course of her treatment she developed huge bluish spots on her tongue and gums, and a few small petechial-like areas in her hands. These were not accompanied by pain and have gradually faded away.

M. C., 38-year-old negro woman, Group III carcinoma of the cervix, was given palliative x-ray last July. Her malignancy progressed and with it she developed severe pain. Although this patient died, the doctor in whose home she worked advised us that she obtained complete relief after the fourth dose of cobra venom.

D. M. D., Group III carcinoma of the cervix, in spite of a series of x-ray treatments developed severe pain. She was given cobra venom by Dr. A. E. Berry, of Mountain View, Oklahoma, without any apparent relief. However, she has been in the hospital since and at the end of a week had not asked for so much as an aspirin; nevertheless she insists her pain is severe. She is being reported as obtaining no relief.

M. E., 40-year-old woman, had a hysterectomy in 1928 and now has a carcinoma of the cervical stump, Group III. Her response to treatment one year ago was gratifying, but she suddenly developed an extensive recurrence, having severe pain in the right thigh, with contracture. Her x-ray was negative for bone metastasis,

and she was admitted for intrathecal alcoholic injections, which were done on two different occasions without relief. She was then given cobra venom and obtained complete relief, in spite of a rapid development of a huge mass in the right side of the abdomen. Following the relief of pain the contracture responded to diathermy and massage.

V. W., a 62-year-old woman, had severe pain sixteen months after treatment for an advanced, Group III, undifferentiated malignancy of the cervix and body of the uterus. She was given cobra venom by Dr. C. E. Northcutt, of Ponca City, Oklahoma, and he reports that she obtained most satisfactory results, and that it was unnecessary for her to use any other drugs for the relief of pain.

B. L., a 37-year-old woman who had a Group IV carcinoma of the cervical stump, obtained no regression from x-ray series. As the growth continued she developed pain, requiring morphine for relief. She was given cobra venom with no appreciable relief. Two alcoholic injections were then given into the spinal canal, with relief for twenty-four hours following the first, and sixteen hours following the second. She is now up and about following a bilateral chordotomy and is completely free of her pelvic pain. This patient is being reported as obtaining no relief from cobra venom.

M. H., a 33-year-old white woman, had a Group IV carcinoma of the cervix. She was given palliative x-ray following which her pain became unbearable and necessitated opiates. She was started on cobra venom and reported her first night's sleep after the fourth dose had been administered. Her relief is estimated as being at least 85 per cent.

M. L., 57-year-old colored woman, was apparently cured with x-ray and radium of a Group III carcinoma of the cervix in 1937. During this time she became addicted to morphine and has taken one-fourth grain four times daily since. A few weeks ago she was brought into the hospital and was taken off the morphine and put on cobra venom. A short time later a vesicovaginal fistula was closed. Patient remained comfortable postoperatively on cobra venom and phenobarbital. When dismissed, she was taking one ampoule every third day.

Encouraged by the results obtained in the relief of pain in pelvic malignancies, I decided to try the remedy in the following cases:

Mrs. H., a nurse's mother, aged 63 years, who was a hopeless cripple from arthritis, was given cobra venom by her daughter and after two days of practically complete relief suddenly took seriously ill with a severe bronchitis. By the time she had recovered from her upper respiratory infection, in spite of the fact she had received her venom every other day, she again developed the pain in her joints and asked that the medication be discontinued. It was discontinued after it had been given twice daily for four consecutive days without further relief.

Mrs. E. H., a doctor's widow, had had diverticulosis of the colon for many years and now had a malignancy of the rectum and lower sigmoid, with constant pain. She vomits after the administration of morphine but can tolerate small doses of hyoscine, morphine, and caetoid compound. She has taken 20 ampoules of cobra venom in a span of fourteen days without any apparent relief.

L. S., a 14-year-old childbirth injury case, with severe pain from muscle spasm, was given 20 ampoules of cobra venom, sometimes receiving two at a time. She received no relief whatsoever and required her same huge doses of barbiturates as before.

The above brief case reports seem to warrant a continued trial of this therapeutic agent. The cobra venom is supplied in 1 c.c. ampoules, each representing 5 mouse units. It was given intramuscularly. The initial dose was $\frac{1}{2}$ c.c., with succeeding daily doses of 1 c.c. until relief was obtained, or until 10 ampoules were given. It should be noted that in 12 of the cases reported the estimated relief of pain ranged from 85 to 100 per cent. While there were no serious untoward sequelae, there were definite local and systemic reactions encountered, manifested by

transitory shock and cerebrovascular disturbances. The use of cobra venom should be limited to carefully chosen cases and its effects closely observed until its physiologic action is better known to the clinician and its ultimate results more clearly defined.

REFERENCES

- Macht, D. I.*: Ann. Int. Med. 11: 1824, 1938. *Gayle, R. F., and Williams, J. N.*: South. M. J. 31: 188, 1938. *Macht, D. I.*: M. Rec. 144: 537, 1936. *Idem*: Am. J. Physiol. 116: 101, 1936. *Rutherford, R. N.*: New England J. Med. 221: 404, 1939. *Black, Wm. T., Jr.*: South. M. J. 33: 432, 1940. *Macht, D. I.*: Science 82: 540, 1935. *Koerbler, Juraj*: Klin. Wehnschr. 13: 1185, 1934. *Prud'homme, E.*: J. de l'Hotel-Dieu de Montreal 4: 372, 1935. *Macht, D. I.*: J. A. M. A. 114: 77, 1940. *Nekula, J.*: Zentralbl. f. Gynäk. 60: 328, 1936. *Macht, D. I.*: Am. J. M. Sc. 189: 520, 1935; Scient. Monthly 47: 34, 1938; Am. J. Physiol. 123: 134, 1938; J. Am. Pharm. A. 26: 16, 1937; Proc. Soc. Exper. Biol. & Med. 35: 316, 1936; Am. J. Physiol. 126: 575, 1939. *Macht, D. I., and Macht, Moses*: Am. J. Physiol. 126: 573, 574, and 575, 1939; *Macht, D. I., and Brooks, Dorothy J.*: Proc. Soc. Exper. Biol. & Med. 41: 418, 1939. *Rottman, Alexander*: Klin. Wehnschr. 16: 1051, 1937. *Macht, D. I.*: Am. Physiol. Soc., 1937; Urol. & Cutan. Rev. 44: 2, 1940. *Macht, D. I., and Macht, Moses B.*: J. Exper. Psychol. 25: No. 5, 1939. *Korbler, J.*: Klin. Wehnschr. 13: 1185, 1934. *Macht, Moses B.*: Proc. Soc. Exper. Biol. & Med. 42: 433, 1939. *Macht, D. I.*: Proc. Nat. Acad. Sc. 22: 61, 1936. *Macht, D. I., and Macht, Moses B.*: Proc. Soc. Exper. Biol. & Med. 42: 428, 1939. *Macht, Moses B.*: Proc. Soc. Exper. Biol. & Med. 42: 436, 1939. *Macht, D. I.*: Med. Press 201: No. 5209, 1939. *Gley, E., and Heymans, J. F.*: Arch. Inter., November 30, 1939. *Taguet, C., and Rousseau, E.*: Prakt. Karzinomblätter, No. 6, 1934.

PREGNANCY COMPLICATED BY TUBOOVARIAN ABSCESS

JOHN C. BROUGHER, M.D., F.A.C.S., VANCOUVER, WASH.

THE early diagnosis of pregnancy has been greatly facilitated by the Aschheim-Zondek test. A negative following a positive test would indicate death of the fetus. The following case report demonstrates such findings complicated by the development of a large abdominal tumor.

Mrs. N., married, aged 22 years, primipara, consulted me Sept. 23, 1938. Her last regular menstrual period began July 5, 1938. On August 1 she had had a light menstrual flow lasting two days. Starting again August 27 she continued to flow for seventeen days, using 4 to 6 pads daily. An Aschheim-Zondek test which had been made September 10 was positive.

Family history revealed three cases of tuberculosis, no diabetes or cancer. Menses began at 12 years of age, regular, twenty-one-day cycle, lasting six days, moderate flow, no clots or leucorrhea, slight pain. An appendectomy for ruptured appendix was done in 1925.

General health had been poor for eight or nine years. As an adolescent she had had various attacks of cystitis and at one time nephritis with albumin. Examination had revealed a pelvic tumor but her father would not permit an operation.

During the past year she had been treated for achlorhydria, retroverted uterus by pessaries, and had been given thyroid for weakness and fatigue. She had been troubled with headaches, vertigo, blurring of vision, and poor appetite. She had palpitations and was very nervous and tired easily. At times she would be quite nauseated. She complained of "soreness in ovaries," indigestion, and constipation.

Physical examination in my office Sept. 23, 1938, revealed a nervous, tall, pale, asthenic individual, appearing to be about 30 years of age, weight 112 pounds (average weight 145), temperature 98.6° F., pulse 80, respiration 20. Other findings

were irrelevant except for pelvic and abdominal findings. The Mantoux test gave a positive reaction but the chest x-ray was negative.

Pelvic examination revealed an anteverted uterus, globular in shape and enlarged to approximately a three months' pregnancy. The isthmus and cervix were soft. Uterus was moderately fixed and pressure caused considerable pain.

On October 2 she had a menstrual period at the regular time and passed some large blood clots but no tissue that looked like placenta. Because of the bleeding, cramps, and lower abdominal pain, it seemed that an abortion was imminent. In an effort to prevent this she was given triweekly doses of antuitrin-S and corpus luteum. Bromides and vitamin B were given to relieve nausea and $\frac{1}{6}$ gr. of morphine sulphate orally for pain as necessary.

Her blood Wassermann on October 10 was negative. Blood count was as follows: Hb 70 per cent; red blood count, 3,260,000; white blood count, 21,800; polymorphonuclear neutrophils, 80 per cent; basophiles, 1 per cent; small leucocytes, 16 per cent; staff cells, 2 per cent; color index, 1. Urine was negative. Vaginal slide was negative for trichomonas or gonorrhea. Basal metabolism was minus 22.

By October 24 her pain had become more severe and rectal palpation revealed cervical dilatation of approximately $1\frac{1}{2}$ cm. and 40 per cent effacement. We were unable to understand why she did not abort. Because of the pain she was hospitalized and consultation held.

On November 10 there was less pain and the smooth outline of the fundus was less tense. Our plan was to let her abort naturally. In order to build up her general condition she was given a transfusion of 500 c.c. of citrated blood followed by another on November 15. Her temperature and pulse remained normal. On November 16 she was improved and left the hospital, her hemoglobin being 88 per cent, red count 4,640,000, and white and differential normal.

By November 18 the patient had noted no movement. The fundus was palpable above the umbilicus. An x-ray showed no fetal structures. In addition to the abdominal cramps, she had now developed severe cramps in both legs and severe pain in the right groin. Rectal examination gave the impression of a 3 cm. dilated cervix inside of which was a bulging fluid-like mass, smooth in outline. The fundus was very tense and felt like a tonic uterus.

On November 25 the patient felt that the fundus was getting smaller and on examination it did prove to be 4 cm. below the umbilicus and the mass was soft except for a nodule at the right of the linea alba just above the symphysis about 6 to 8 cm. in diameter. The laboratory report was hemoglobin 100 per cent; red cells, 4,180,000. Serum calcium was 10 mg. and blood phosphate 3.5 mg. per 100 c.c. of whole blood.

After decreasing in size the fundus again enlarged. Leg cramps, numbness, and lower abdominal pain increased in severity so that codeine sulphate was necessary to relieve pain. On December 9 she had a slight bloody show and severe pain which did not simulate uterine contractions. The feet were swollen and the patient weighed only 112 pounds. Abdominal examination showed the presence of a hard tumor as before described, and a laparotomy was decided upon. Consultant considered the tumor mass to be a fibroid of the uterus with a cystic mass related to a pelvic organ but extrauterine.

On December 10, the patient was given 500 c.c. of citrated blood. Salpingograms made before the operation revealed a large soft tissue extrauterine tumor. Laparotomy was performed December 12 and was followed by another injection of 500 c.c. of citrated blood.

Operation.—Bilateral salpingectomy and oophorectomy.

Findings.—There was a large firm tumor mass extending in the midline above the umbilicus containing a clear yellowish gelatinous material in the upper portion. The uterus was pushed far down in the right side of the pelvis. The mass was found to have its origin in the left tube and ovary. The right tube and ovary were bound up in a tight mass about 6 by 8 cm. in diameter.

The abdomen was opened through a suprapubic midline incision. By careful blunt and sharp dissection the mass was freed in all portions except deep poste-

riorly. When gentle traction was placed upon the cyst, it ruptured and was found to contain perhaps 1,500 c.c. of greenish foul pus. The cystic mass was removed leaving a thick wall of granulation tissue. The uterus was identified; the right tube and ovary were removed except for a portion of the ovary which was left attached to the tuboovarian ligament. A portion of the cyst cavity was obliterated with sutures of plain catgut. Four cigarette drains were placed into the pelvis, and the abdominal wall was closed in layers.

Pathologic Report.—Dec. 12, 1938: Specimen consisted of the wall of a cyst which had measured approximately 12 to 15 cm. in diameter. The lining was plastered with masses of coagulated purulent-appearing exudate, and beneath the exudate the lining membrane of the cyst presented a papillomatous appearance; the surface had a velvety appearance and was covered with many small papillomas $\frac{1}{2}$ to 1 mm. in diameter. The outer wall was thickened and fibrous and revealed many adhesions.

A second mass 6 cm. in diameter revealed a further cystic growth, apparently a Fallopian tube. The lumen was distended and the mucosa revealed a yellowish pigmentation.

Microscopic sections through the wall of the cyst revealed inflammatory infiltration throughout all areas. There was a papillary proliferation of the lining membrane characterized by a rather dense fibrous stroma and continuation of dense inflammatory changes in several areas. Sections through the wall of the cyst revealed infiltration of large deeply-staining cells apparently originating from the lining epithelium of the cyst cells extending outward into the wall of the cyst and scattered in small masses and clumps through the tissue interstices. The picture was not definitely that of malignant growth. Further study of paraffin sections reveals no evidence of any malignancy.

Diagnosis.—Papillary cystadenoma of the ovary with marked inflammatory changes; salpingitis.

The pus was cultured and a guinea pig was injected to rule out an acid fast organism as the cause of such a low grade inflammatory process but the tests were negative.

Laboratory Report.—Smear and culture of light green pus obtained from right Fallopian tube and amber colored fluid from left tube: Gram's stain: Slide was loaded with disintegrating pus cells. There were gram-positive diplococci, sometimes almost bacillary in form, often seen in chains. Bacteria did not stain typically and appeared to be partly dissolved. Seventy-two-hour culture, no bacteria found. Acid fast smear for tuberculosis, none found.

Direct smear from right tube revealed many leucocytes and a few gram-negative bacilli. Cultures seventy-two hours, no bacteria found.

Progress.—There was a profuse serosanguineous drainage for four days. The postoperative condition was good until December 14 when the patient became quite toxic and had a white blood count of 49,500, a differential count of small lymphocytes 4 per cent, large mononuclears 2 per cent, neutrophils 93 per cent, eosinophiles 1 per cent, staff cells 12 per cent, and vacuolated cells 2 per cent. She was given another 500 c.c. of citrated blood and from then on the blood count and temperature dropped. She was afebrile after the fourth postoperative day and the white count dropped to 19,500 on the sixth, and to 14,900 on the twelfth postoperative day when she was discharged from the hospital. The wound drained a bloody fluid for ten days and then gradually the drainage became serous and the wound was entirely healed by February 3. Her weight had increased from 95 pounds to 107 during this period.

The pelvic wall of plastic exudate surrounding the pyosalpinx was gradually absorbed until the abdomen became soft and normal to palpation. Six weeks after the operation pelvic examination revealed an anteverted, moderately fixed uterus with no parametrial tenderness. The cervix was clean. After two months she had ovarian deficiency symptoms necessitating estrogenic hormone injections. One milligram tablet of stilbestrol daily also relieved her of the hot flushes.

SUMMARY

This case has been reported because of the unusual size of the left tube and ovary. One may be criticized for the time element in waiting for surgical intervention, but again the time element may have saved her life by allowing nature to wall off securely and immunize the peritoneal cavity against the invading organism. The cul-de-sac could have been needled and the pus evacuated through the vagina; however, the afebrile course gave no indication of a purulent process.

410 ARTS BUILDING

PREGNANCY AND FEVER THERAPY

JOHANN R. MARX, M.D., INGLESIDE, NEB.

(From the Hastings State Hospital)

THE following case is presented because of a successfully tolerated pregnancy during the full course of artificial fever therapy for general paresis.

Mrs. G. M., a white, 36-year-old, married female had been essentially well until approximately ten years ago at which time a positive blood Wassermann revealed syphilis. There was no history of primary or secondary syphilitic lesions. She had received regular treatment with arsenicals and heavy metals ever since. The blood serology changed frequently from positive to negative during the course of the years but remained positive for the last two years despite all chemotherapy. She gave birth to four children whose cord blood was checked for syphilis at the time of delivery and found to be negative, except in the last child which is now one year old. There was no history of abortions or miscarriages.

During the last six months the patient became increasingly forgetful, careless about her appearance and conduct, exhibited bewilderment, and complained of headaches. She experienced difficulties when walking in the dark, and complained of occasional momentary periods of blindness. Immediately before admission to this hospital in September, 1939, she had received three fever treatments in a private hospital.

The examination on admission showed typical mental and physical symptoms indicative of general paresis which diagnosis was confirmed by positive blood and spinal serology and paretic gold curve.

On Oct. 6, 1939, the patient was started on artificial fever therapy in the Kettering Hypertherm. The first three treatments of five hours at a temperature of 105° F. to 106° F. once weekly, were satisfactorily tolerated. The patient was extremely cooperative, and there were no complications with the exception of some nausea. During the fourth treatment, the patient complained of pain and cramps in her abdomen. These, however, disappeared at the end of the treatment. During the following two treatments, the patient's nausea increased considerably; she experienced repeated voluminous emesis. A physical examination at that time revealed the presence of a pregnancy of approximately three months' duration. It was impossible to obtain any reliable data from the patient about her last menstrual period. Although pregnancy is considered as a contraindication to fever therapy, it was decided to continue the patient's course with increased precautions. The length of the treatments was shortened to three hours and thiamine chloride was administered intravenously.* The treatments under that regime were tolerated much easier than the previous ones, and the nausea and emesis disappeared almost completely. During a few of the treatments, the patient exhibited mild symptoms of tetany which were successfully remedied by maintaining the patient on an increased calcium-gluconate medication.

*20 mg. "crysto-vibex" during the fever and the two preceding days.

These can be taken only late in pregnancy, up to seventy days before delivery. Seventy records on 52 patients were taken and the fetal waves showed in 87 per cent. They state, "The faster the pulse of the mother, the faster is that of the fetus and vice versa." Lian, Golblin and Minot⁵ examined fetal hearts by graphic methods (the number is not stated) and found the duration of the systoles to be 0.16 second and the diastoles from 0.16 to 0.19 second. The first sounds were 0.06 and the second 0.05 second in length while the second was greater in amplitude. Usually the sounds, due to reduplication of the first, were in three parts when heard through the loud speaker. They also state, "We have been able, further, to cut a few records." Pommerenke and Bishop⁶ report they have made a few disc records of fetal heart sounds and have continuously made audible the fetal heart sounds in the delivery room. Mathews⁷ has developed an apparatus for broadcasting fetal heart sounds during delivery but makes no statement as to permanent records. DeCosta⁸ has developed what he calls a photostethoscope which changes sound into flickers of light, thus the fetal heart sounds are followed by observing the light flickers. Orias and Braun-Menendez⁹ state the recording of fetal heart sounds is very difficult and this explains why so few of such studies have been made. They have included 2 fetal heart sound tracings made by Periera which are very good. They mention the graphs of Hofbauer and Weiss¹⁰ (1908) and Beruti¹¹ (1923) but say these are not clear enough to distinguish the vibrations.

METHODS USED IN PRESENT STUDY

By means of the stethograph, the fetal heart sounds were photographed on a moving film simultaneously with the mother's electrocardiogram (Leads I and II) and pulse, thus showing the rates and rhythms of each and the rate relation between the fetal and maternal hearts. With the third lead, the mother's heart sounds were stethographed. These records admit of accurate measurement of fetal heart rates, of duration of the sounds, of duration of systole and diastole and observation of the fetal rhythm. By measuring the deflections in the electrocardiogram, the exact rate of the mother's heart is known.

After the above recordings, the fetal and maternal heart sounds were recorded on the same disc. This admits of careful study (at slow or normal speed) of these sounds, of murmurs and any change in rhythm. Since heart sounds of different persons have their own peculiar quality characteristics (somewhat as voices do), these can be preserved and can be reproduced with all the tone peculiarities.

After recording, the heart sounds were studied when audited through the loud speaker and many variations were heard that were not recorded in the stethograms or the discs.

THE STETHOGRAPH

The stethograms of the fetal heart sounds were taken by means of the stethograph developed and reported by Bierring, Bone, and Lockhart¹² in 1935. Technical and constructional details of this instrument are given in their article.

The stethograms of all fetal heart tones shown are recorded at the rate of 25 mm. per second so longer strips may be viewed and the many variations of the sounds can thus be seen.

DESCRIPTION OF THE CARDIOPHONOGRAPH

The cardiophonograph, developed by one of us (A. L. S.), is employed to amplify the heart sounds so they may be heard through a stethophone or a loud speaker and then recorded on special phonographic discs. All mothers' heart sounds were recorded on the same disc with the fetal heart sounds, each occupying about one-half the record.

At times the sounds are hardly discernible in the stethogram and are hardly audible in the disc recordings. In three cases the fetal heart sounds could not be heard through the acoustic stethoscope but were successfully recorded and reproduced.

an adequate pelvis. It proved necessary to do a bilateral cleidotomy which quickly facilitated the delivery of the shoulders. After the shoulders and head had been delivered and the amniotic fluid drained off, examination showed that there was still a large abdominal tumor. This tumor prevented the extraction of the fetus. An attempt to enter the uterus with the gloved hand and arm was quite difficult, but was accomplished by partially crushing the chest of the dead fetus. A large fetal abdomen was felt. This was punctured with Smellie's scissors and a large amount of clear yellow fluid containing some fibrin flakes drained out. The fetus then delivered spontaneously. After the placenta had been delivered and the episiotomy repaired, the fetal abdomen was examined through an incision. The bladder, intestines, and liver were grossly normal; the kidneys were abnormally small, measuring not over 3 cm. in length.

The postoperative course was complicated by three chills, the only objective findings being a tender uterus. Treatment consisted of oxytocics and blood transfusions. The patient was discharged on the thirteenth post-partum day.

Dorland¹ divides cases of watery accumulations in the peritoneal cavity into six types, including serum in fetal peritoneal cavity (true fetal ascites), urine distending urinary tract of fetus (fetal urinary retention), fluid throughout the tissue of fetus (general anasarca of fetus), cystic degeneration of renal structure (congenital polycystic kidneys), cystic degeneration of fetal liver, and fluid distending genital tract of fetus. In all probability the case reported represents a case of true fetal ascites. Although a diagnosis of abnormality was not made, it was suspected from the rapid growth of the uterus in the last six weeks of pregnancy.

REFERENCE

- (1) *Dorland, W. A. Newman: Am. J. Obst. & Dis. Wom. & Child. 79: 474, 1919.*

A NEW FORCEPS POSSESSING A SLIDING LOCK, MODIFIED FENESTRA, WITH IMPROVED HANDLE AND AXIS TRACTION ATTACHMENT

RALPH LUIKART, M.D., F.A.C.S., OMAHA, NEB.

(From the Department of Obstetrics and Gynecology, Creighton University School of Medicine)

THE purpose for which the obstetric forceps was originally devised was to extract the fetus by the head without damage to either mother or child. As stated by De Lee, "As soon as the right of either is encroached upon, the instrument ceases to be the forceps of obstetrics and becomes simply an instrument of extraction similar to the craniotomy forceps and not so good." It is evident that an instrument simple in design and as nearly foolproof as possible should be the instrument of choice in the hands of novice or expert. If the functional capacity of the instruments used can be improved and their use made safer additional service is rendered to the patient. I believe the forceps here described embodies such improvements.

This forceps embraces three safety features: (1) the Kjelland type sliding lock, (2) modification of the fenestra by closing it on the pelvic side, and (3) one shank extended down and a part of one handle. This modification of the handle reduces the danger of excessive pressure of the blades on the fetal head and is applicable to all Kjelland type forceps, and such forceps would be definitely improved by incorporating this safer handle. The blades have a conventional pelvic curve and well-shaped cephalic curve.

In combination with the fever treatments the patient received mapharsen and bis-muth salicylate which were continued after the termination of the fever. The pregnancy continued without any difficulties while the patient completed fifty hours of fever in thirteen treatments. A serology check in March, 1940, showed essentially the same findings as before the fever therapy, except that the spinal Wassermann changed from a strong positive to a weak positive. The patient's mental and physical condition showed no remarkable changes except for improvement in walking.

On April 15, 1940, the patient gave birth to a living boy in a quick and uncomplicated delivery. The child weighed 7 pounds 8 ounces and showed no physical abnormalities. The Wassermann determination on the cord blood of this child returned negative.

The case appears instructive because a full course of artificial fever therapy was completed on a pregnant woman without any ill effects to the pregnancy or mother. The intravenous administration of thiamine chloride appeared useful in relieving hyperemesis. It may be considered a result of the combined fever and chemotherapy that the child's Wassermann was negative, while the preceding child had been afflicted with congenital syphilis despite continuous chemotherapy of the mother during pregnancy.

SUMMARY

A case of general paresis is presented in which artificial fever treatment was carried out successfully without interference with an existing pregnancy.

The child showed no signs of physical damage from either fever therapy or syphilis. Its cord blood Wassermann was negative despite positive blood and spinal serology of the mother.

OBSTRUCTED LABOR DUE TO FETAL ASCITES

EUGENE T. ELLISON, M.D., NASHVILLE, TENN.

(From The Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine)

THE following case of fetal ascites is reported because of the rarity of this condition and because certain of the mother's prenatal physical findings suggested abnormal uterine contents.

Mrs. L. L., aged 21 years, weight 154 pounds, primipara, entered the hospital approximately five weeks before term, with chief complaint of aching in the side and back, associated with dysuria. The pregnancy had been uneventful until five weeks previously. Forty-eight hours before admission she had a chill. Examination on admission revealed left costovertebral tenderness; uterus was the size of a seven and a half months' pregnancy, with position L.O.A., head floating. Temperature was 101.2° F. Urinalysis showed numerous clumped white blood cells, 3-plus albumin, and bacteria; when cultured, the bacteria proved to be *B. coli communis*. The blood showed 8.2 Gm. hemoglobin and 3,100,000 red blood cells. Wassermann was negative.

The treatment consisted of multiple transfusions, forcing of fluids and acidification of urine. She was discharged, improved, ten days after admission. She re-entered the hospital two weeks later, two weeks from term, with a history of leaking a small amount of amniotic fluid. Examination at this time revealed a striking enlargement of the uterus over that found on previous examination. She continued to leak fluid slowly for two days and then went into active labor, with crowning of the fetal head in ten hours. The head was delivered with low forceps after an episiotomy. The shoulders seemed to be caught tightly by what was known to be

The forceps above described, combined with the axis traction attachment, satisfactorily fulfills every need for traction, at the same time assuring the greatest possible margin of safety. When, however, it is necessary to apply forceps to an aftercoming head the Luikart-Kjelland forceps² is preferable because, like the Piper forceps, it has no pelvic curve, and in addition possesses the safety factor of the closed fenestra.

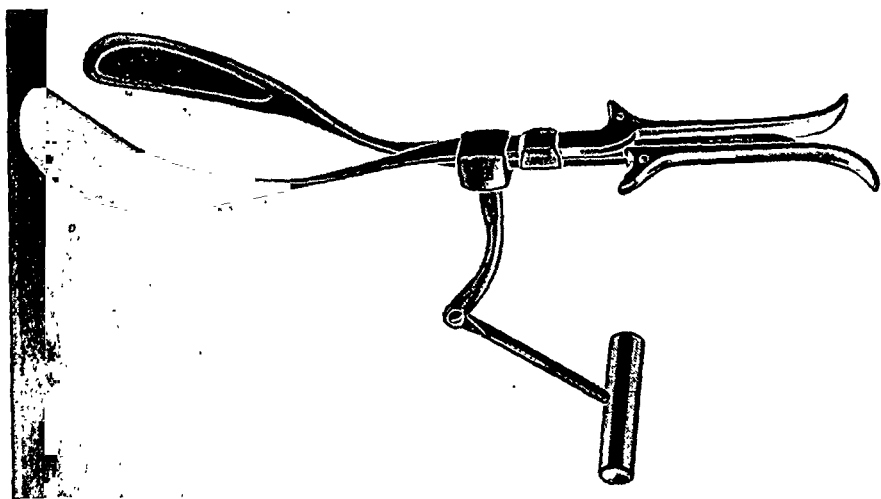


Fig. 3.—Luikart forceps and axis traction attachment. Note standard pelvic and cephalic curves of blades, closed fenestra, sliding lock, modified left handle, axis traction, showing simplicity of attachment and direction pointer.

Hence, these two forceps (the type described in this paper and the Luikart-Kjelland type) and the axis traction attachment should completely fill an obstetrician's needs for forceps, at the same time offering the greatest margin of safety in each operation.

I wish to acknowledge with thanks assistance given by J. Sklar and Company, Long Island City, N. Y., by Dr. Ralph Reese of Chicago and Dr. Maurice E. Grier, of Omaha, for suggestions in regard to the handle modification and by Dr. Frank Murphy of Omaha for assistance in the photography.

REFERENCES

- (1) Bill, A. H.: Am. J. Obst. Gynec. 9: 606, 1925. (2) Luikart, Ralph: Ibid. 34: 686, 1937.

Kirchner, W.: Intravenous Narcosis in Obstetrics, Med. Klin. 35: 1342, 1939.

Kirchner emphasizes that the administration of an intravenous narcotic is as much of a hardship on a pregnant woman as any other anesthetic. For a long time he has used the typical morphine-scopolamine twilight sleep to which he has added pernocton and also dilaudid. When evipan was introduced as an intravenous anesthetic he began to make use of it. This drug proved to be helpful for obstetric operations except cesarean section, and version and extraction. Evipan proved useful also in eclampsia regardless of whether the convulsions occurred during pregnancy, labor or after delivery. It is generally believed that evipan has no deleterious effect on the baby although some authors believe the babies are born asphyxiated and remain drowsy for a few days after birth.

Evipan has no effect on uterine contractions during labor. However, since this drug may have a bad effect on the uterus in the third stage, it is recommended that small doses of pituitary extract be given with this drug.

J. P. GREENHILL

Occasionally the only possible position in which the forceps blades can be applied is with one blade over the right or left side of the posterior parietal and the other blade over the left or right malar bone. Less often, but by necessity it does happen, that an anteroposterior application is the only application possible, or it is made by mistake. In either of the above applications, when the forceps is locked and traction attempted, the tip of one blade presses into the malar bone or the bridge of the nose, as the case may be. This very unfavorable pressure, which may endanger the life of the fetus, can be avoided by use of the forceps here described,



Fig. 1.

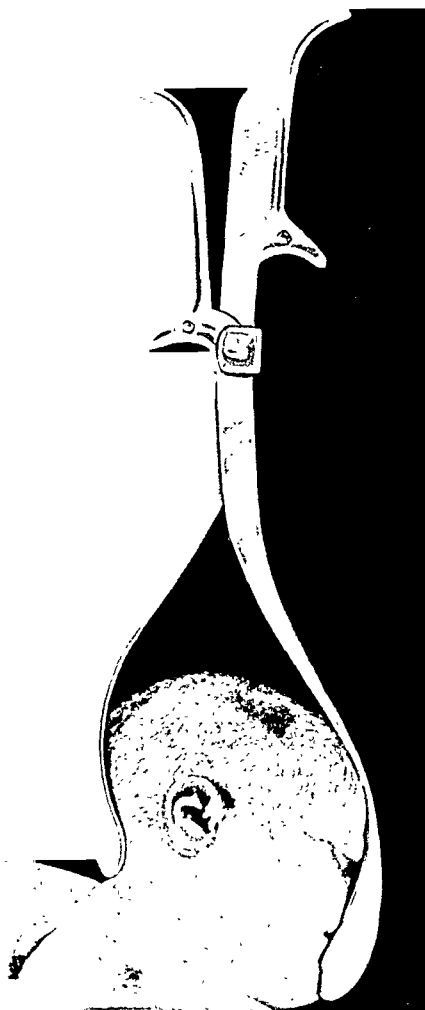


Fig. 2.

Fig. 1.—Conventional Simpson forceps, revealing a pelvic application to a transverse presentation of the fetal head. Note pressure over nasal bridge.

Fig. 2.—Same application of forceps as shown in Fig. 1. Note advantages of sliding lock when this application is made by necessity or accident. The fit of the forceps is perfect. No spring in shank or blade is needed.

because of its Kjelland type sliding lock. Furthermore, this safety feature reduces the necessity for spring in either the shank or the blades. In fact, the rigidity of the blades decreases the likelihood of the forceps slipping, hence the danger of damage to the fetus is reduced.

The axis traction apparatus is a modification of Dr. A. H. Bill's¹ and McClintock's axis traction attachments. This attachment is simple, is easily applied, and has the direction pointer suggested by Bill. My experience with its use has been extremely satisfactory. It can be used to considerable advantage in the Scanzoni maneuver as described by Bill.

Obstetrics

This comprehensive presentation of *Obstetrics and Gynecology*⁴ in two volumes of approximately one thousand pages each, is offered by some sixty members of the staff of the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-In Hospital under the editorship of Dr. Adair. The unity as well as quality of the two subjects has been recognized, and the text offers a logical consideration of both specialties, as well as their relationships to other branches of medicine. Although the major portion of the work is devoted to obstetrics, the subject of gynecology by no means has been overlooked and the fundamental principles of the abnormalities of the nonpregnant state are thoroughly described. The introductory chapter quickly sums up the modern views of reproduction, the physiology and pathology of the pelvic organs, and presents a general statement of the broad aspects of this branch of medical practice.

The basic biology of the human female continues with general statements on the physiology and anatomy of the generative organs, malignancy and the mechanism of infection and immunity. In a similar manner therapy of various modes in relation to both the reproductive cycle and the nonpregnant organs is offered. The introductory section also deals with nutritional requirements in both normal and abnormal conditions.

The editor's broad vision and a wide knowledge of communal and individual problems is reflected in his very full discussion of maternal care, morbidity, mortality, and the limitations of human reproduction. The life cycle of the human female carries this individual from germ plasma to retrogressive changes of post-reproductive life. This section is extended to include such complications as sterility, infertility, and deviations of marital physiology.

Pregnancy and its abnormalities lead from the anatomy, physiology, and hygiene of the nonpregnant to that of the pregnant woman with a discussion of the diagnosis of pregnancy, early termination, abnormal situation, and early and late toxemias of pregnancy. In the latter section on the late toxemias of pregnancy, one finds an extensive presentation of the subject, a wide review of the literature and a recapitulation of the extensive clinical and laboratory research on the toxemias of pregnancy which has emanated from the Lying-In Hospital of Chicago during the past decade. In discussing the parturient woman, a similar logical sequence is used. The mechanism and management of normal labor is followed by a discussion of the third stage. Realizing that the major portion of obstetrics in the United States is not carried out in the narrow confines of the hospital delivery room, the editor has offered a short, but, thoroughly developed plan and technique for home delivery. Concise directions and suggestions for the treatment under emergency circumstances of the various complications of labor, hemorrhage, shock, toxemia, and abnormal situations in regard to the newborn infant are given.

The text continues with the pathology of labor, management of breech and other abnormal attitudes. Such evidence of pathologic labor, as premature labor, prolonged labor, and the cord dystocias are discussed fully and followed by the fetal phases, the abnormalities of which lead to antenatal and intrapartum death. In discussing placenta previa, the need for smooth organization of the hospital in handling hemorrhage is stressed. The value of the transfusion, the success of blood banks, and the various methods of vaginal approach to placenta previa are described. In spite of its possible attendant hemorrhage the lower segment operation is favored for abdominal delivery in placenta previa.

As the treatise continues in the second volume, the problems of the puerperium and the newborn infant are discussed. The problems of pelvic regeneration and repair are followed by the nursing care of the puerperal woman. Puerperal infection is regarded as a contact wound infection, and those with hemolytic streptococcus as practically always exogenous. The therapeutic effect of sulfanilamide in such

⁴*Obstetrics and Gynecology.* By the Departmental Staff of the University of Chicago and Other Contributors. Edited by Fred L. Adair, Mary Campau Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology, in the University of Chicago, etc. Volume I, 1000 pages with 359 engravings and 14 plates. Volume II, 1031 pages with 304 engravings and 10 plates. Lea & Febiger, Philadelphia, 1940.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

Greenhill's *Office Gynecology*¹ is a useful book which should prove of value, particularly to the general practitioner and the budding specialist, as it contains many hints and suggestions valuable in office treatment, including such common measures as the vaginal douche, vaginal pessaries, and the treatment of diseases encountered in gynecologic practice. The chapters on gynecologic and obstetric endocrinology, and menstrual irregularities are likewise of real interest. Whether the colposcope should have been included in office gynecology might well be doubted, nor can I agree that intraspinal (subarachnoid) injection of alcohol for pain due to carcinoma of the genitalia, as well as curettage and transabdominal pneumoperitoneum, should be considered office procedures.

—R. T. Frank.

The fifth edition of Young's *Textbook of Gynaecology*² has appeared. The first edition was published in 1921. With each edition the text has become more crystallized and is as always, short, clear, sound, and the book is well illustrated. One can see the refinements which successive revisions have made possible. In the present edition, particular attention has been paid to the physiology of the sex organs and the newer understanding of the sex hormones, which are really very well presented, even if some small inaccuracies have crept in. This is a very valuable, short textbook. It may be stated that a few improvements could be made, as, for instance, in the classification of ovarian growths, which is distinctly crude. Tight plugging of the vagina for puberty bleeding, as a routine measure, would not be accepted in the United States.

R. T. Frank.

Martius' *Gynecologic Operations*,³ which was reviewed in these columns in 1937, has now been translated into English. At that time a very appreciative and laudatory review was given to this valuable contribution to operative gynecology. The illustrations in the original German and in the present American edition are identical, and are noteworthy for their simplicity and striking qualities. No better operative gynecology in short compass is available. The descriptions of operations are clear-cut and sufficiently detailed to be useful, both to the general surgeon and the specialist. While the translation is quite understandable, the English is frequently awkward, even if accurate. In spite of this defect, the book should prove of great value to both student and operator.

—R. T. Frank.

¹*Office Gynecology*. By J. P. Greenhill, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, etc., Chicago, Ill. With 106 illustrations, 406 pages. The Year Book Publishers, Inc., Chicago, Ill., 1939.

²*Textbook of Gynaecology*. By James Young, Professor of Obstetrics and Gynaecology, University of London, etc. Fifth edition, with 226 illustrations, 425 pages. Adam and Charles Black, Soho Square, London, 1939.

³*Gynecologic Operations and Their Topographic-Anatomic Fundamentals*. By Professor Dr. Heinrich Martius, director of Women's Clinic in Göttingen. Authorized English Translation by W. A. Newman Dorland, M.D. With 404 mostly colored illustrations, 486 pages. S. B. Bebour, Publishers. Chicago, 1939.

Lying-In Hospital are appended and the book is completed with a brief discussion of the relationship of vital statistics to obstetric and gynecologic practice, with some definitions and a presentation of the coding of puerperal deaths agreed upon for the present decade at a recent meeting of the International Commission on Causes of Death.

The two volumes represent a thoughtful consideration and excellently balanced presentation of the principles of the two specialties. The logical development of the text with an avoidance of duplication and the extended consideration of the broad aspects and interrelationships with the basic sciences and other clinical entities makes these two volumes a reference work of unusual merit and value which may be highly recommended.

—Philip F. Williams.

The title of this volume, *The Management of Obstetric Difficulties*⁵ does not indicate its scope; it is actually a complete textbook of obstetrics for practitioners. It differs from a textbook for medical students as a clinical paper differs from a medical editorial. The discussions come directly to the point, historical background is mentioned but minimized, little space is given to facts of academic interest only; discussions of therapy are followed by a detailed tabulation of recommendations. The author does not say, "Sedation is indicated," he specifies what, and how much, and how it is to be given. His entire book is pleasantly free of vagueness. The preface states, "I favor the expression of my own preferences in undecided issues" and this policy has been skillfully carried out. The author's personal views are clearly, but unobtrusively, presented as his own. In general substance the work is sound; to follow its precepts would be to practice safe obstetrics.

Adverse criticism of so good a work seems a little unkind. Yet it is true of this book, as of many others in medicine, that the services of a professional grammarian would add polish and reduce verbiage. Occasionally an explanation is overworked. For example, pelvic hyperemia in pregnancy is given as a cause for deposition of fat on the hips, for symphysial separation, and for increased susceptibility to trichomonas infection.

The volume is recommended to general practitioners, graduate students, and men preparing for the American Board examination. Even the experienced obstetrician will find it worth reading. Especially useful are the references to recent and important literature.

—Pendleton Tompkins.

The conception of this joint volume, *Obstetrics and Gynaecology*,⁶ was based on the feeling of the original editorial board that these two subjects should be combined in teaching as well as in practice, and an excellent chapter is devoted to the nature of the correlation. Some changes in the authorship have been occasioned by death, and in the present editorial board, headed by Kerr, faculties of obstetrics and gynecology of Glasgow, Aberdeen and Edinburgh are represented.

The book retains the form and subject content of the two previous editions. In the revisions there has been incorporated new material with regard to the physiology of the reproductive organs and an excellent treatise on nutrition, full consideration of chemotherapy of infections, a discussion of the more recently described ovarian tumors. The section on radiology and roentgen technique in obstetrics and gynecology, re-written by a new contributor, includes references to much of the recent literature.

As expressed in the previous reviews of this volume, it must be considered an excellent combined textbook of the two subjects, not only for the student but for

⁵*Management of Obstetric Difficulties.* By Paul Titus, Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh, etc. Second edition, 868 pages, with 368 illustrations and 5 color plates. The C. V. Mosby Company, St. Louis, 1940.

⁶*Combined Textbook of Obstetrics and Gynecology.* Revised and rewritten by J. M. Munro Kerr, R. W. Johnstone, James Hendry, Dugald Baird, James Young, Donald McIntyre, E. Chalmers Fahmy, with additional contributions by Charles McNeil and G. Jackson Wilson. Third edition, 1192 pages with 499 illustrations and numerous x-ray plates. Williams and Wilkins Company, Baltimore, 1939.

conditions is cautiously evaluated. Obstetric facts in end results, child growth and development are succinctly stated. Stress is laid on the care of the premature. The diseases of the newborn are discussed not only from a medical and surgical standpoint, including congenital deformities and orthopedic lesions, but also such conditions as asphyxia and birth trauma.

Taking up in an extended manner the gynecologic conditions previously referred to in various places of the text, the neoplastic diseases are first considered.

The incidence of cervical stump carcinoma following subtotal hysterectomy for myoma is regarded as counterbalancing the higher mortality of the total operation. Here the intrauterine application of radium is considered preferable to the use of x-ray in nonoperative treatment. The discussion of uterine carcinoma is extensive, various methods of classification and grading are included. The more recently differentiated ovarian tumors are fully described. The choice and nature of the operation to be performed in endometriosis is well analyzed. In discussing cystic degeneration of the chorionic villi and the malignant process which may follow, the text suggests that in view of the radiosensitivity of chorionepithelioma, irradiation should be carried out in conjunction with operation. Gynecologic displacements and relaxations are dealt with particularly in regard to obstetric prophylaxis of the lesions. It is concluded that no single method of operative therapy is adapted to all forms of genital prolapse. In a similar manner the end results of obstetric infections on the pelvic tissues is described.

Gonorrhea is considered from both its obstetric and gynecologic aspects, its relationship to fertility as well as to pregnancy. In discussing the treatment of gonorrhea by sulfanilamide, the text suggests that the fetus may be more susceptible to this drug than the mother. Although syphilis is discussed mainly from the standpoint of its relationship to reproduction, no suggestions as to treatment occur here, and it is only later in the section on internal medicine that one picks up the therapy of syphilis during pregnancy.

Tuberculosis is considered both from the standpoint of its genital lesions and by a consideration of the treatment of the woman with pulmonary tuberculosis who becomes pregnant. Early abortion is recommended for active tuberculosis, but otherwise general lines of treatment with only indicated obstetric surgery are suggested.

The most recent plan of treatment of trichomonas infestation in the Chicago Lying-In Hospital consists in the use of lactose intravaginally to replace the depleted carbohydrate state of the vaginal mucosa and thus effect a return of the normal vaginal flora and acidity. In a discussion of chronic cervicitis, judgment has been reserved on conization and electrocoagulation because of tissue destruction and scarring.

The third section in this volume consists of a discussion of the relationship of various medical and surgical diseases to reproduction in its various phases as well as to function of the pelvic organs. This section also includes an ample presentation of roentgenologic diagnosis in obstetrics especially with reference to pelvimetry and fetometry.

The final section discusses pre- and postoperative management of obstetric and gynecologic procedures according to the schedule used in this Chicago clinic. It is followed by an excellent chapter on the subject of intravenous therapy and blood transfusions, with a discussion of the banking of blood and its derivatives. Anesthetic agents and methods are discussed. In this section, the authors have included a consideration of the various methods of amnesia-analgesia during labor. This particular chapter is marked by an unusual degree of detail in treating the subject.

There is a very concise presentation of cesarean section with excellent illustrations of the lower segment operation. There is an excellent recapitulation of morbidity and mortality of cesarean section. The chapter on hysterectomy is followed by a presentation of version and forceps deliveries, and a short discussion of the destructive operations.

An appendix giving various types of diets which might be used in the obstetric-gynecologic services with details as to menus and food values is a valuable addition. The techniques of many clinical laboratory tests used in routine work in the Chicago

In *Obstetrical Manikin Practice*,¹⁰ Dr. McNeile has developed teaching material for six seminars. This demonstration course is offered to supplement clinical material and to offer the student an opportunity to try out various procedures which he may have seen performed in clinic. In addition to various obstetric operations through the vaginal route there has been included a demonstration of the mechanism of labor in abnormal pelvis which may do much toward assisting a student in an understanding of the physics of parturition.

—Philip F. Williams.

Dr. Marshall in this monograph *Caesarean Section, Lower Segment Operation*,¹¹ strongly emphasizes the advantages of this procedure. He has performed some 250 such operations, and may be regarded as well qualified to discuss its advantages, technique, and dangers.

Opening with an interesting and carefully documented history of the early suggestions and later attempts at the operation, he discusses the improvements in bacteriologic and surgical technique which made possible the procedure of today. He discusses the types of anesthesia available, and concludes that local anesthesia should be much more widely employed; that ether should be reserved for cases of great urgency, while spinal should be used in a few cases in whom considerable technical troubles can be foreseen. The physiology of the development of the lower uterine segment and the nature of the incision and technique of this type of operation, well illustrated, is comprehensively discussed. In view of the fact that this operation is often undertaken in the presence of infection in a pregnant woman, the author has stressed the various protective procedures against infection such as vaginal antisepsis, care of the field of operation, method of peritonization of the incision and drainage of the uterus and peritoneal cavity and of the abdominal incision.

In consideration of Doerfler's operation he withholds judgment on the suggested eversion of the uterus. The treatment of hemorrhage and the use of oxytocics are considered, and there is a discussion of the use of this type of operation for placenta previa. He does not ascribe any superiority to the lower segment operation over the classical one in the treatment of placenta previa unless there is a concomitant infection. The various potentialities for evil results of the operation are mentioned as are suggestions as to how to obviate them.

In closing the monograph he states that there was an unreduced maternal mortality of 0.0 per cent, unreduced fetal mortality of 5.7 per cent, and total morbidity rate of 23.5 per cent in his series. In 246 operations, 70 were performed for suspect of present infection, 43 for placenta previa, 19 for toxemia, 14 for heart disease. The results are surprisingly favorable in view of such a large proportion of poor operative risks. A splendid consideration of an operation with a constantly widening use.

—Philip F. Williams.

*Normal Obstetrics*¹² by Raul Briquet is a well-organized and documented general obstetrics. Particular emphasis has been placed on the physiology and pathology of conditions. The book is fully up to date. The author has incorporated and utilized the best from European and American literature. The 423 illustrations are excellent, the majority from classic and well-known sources, to whom due credit has been given.

—R. T. Frank.

¹⁰*Obstetrical Manikin Practice*. By Lyle G. McNeile, Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, etc. With 38 illustrations, 111 pages. Williams and Wilkins Company, Baltimore, 1939.

¹¹*Caesarean Section, Lower Segment Operation*. By C. McIntosh Marshall, Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. With 2 plates and 107 illustrations, 230 pages. Williams and Wilkins Company, Baltimore, 1939.

¹²*Obstetricia Normal*. Professor Raul Briquet, lente catedrático de Clínica Obstétrica e Puericultura Neonatal da Universidade de S. Paulo. Com 427 figuras das quais 37 em duas e mais cores. Livraria Editora Freitas Bastos, Rio de Janeiro, 1939.

the general practitioner as well. If any criticism could be offered it would be that the discussion of gynecologic operations was exceedingly brief. This, however, is explained in the attitude of the authors that surgical technique in the treatment of women cannot be based on book reading but requires a long clinical apprenticeship.

—Philip F. Williams.

Exhaustion of the first edition within a relatively short time offered Beck the opportunity to thoroughly revise his excellent *Obstetrical Practice*,⁷ particularly by the addition of much new material, e.g., a new chapter on retained and adherent placenta. There are two features which clearly distinguish this volume from similar texts, namely the large number of instructive, mostly diagrammatic illustrations, and the inclusion of an unusual amount of detail information, such as average percentage saturation with oxygen of blood coming from the uterus; maternal placental blood pressure; differences in blood constitution of mother and fetus; nitrogen and calcium storage, etc. The discussion of adequate food supply during pregnancy includes two and one-half pages of tables giving protein, carbohydrate, fat, calcium, iron and vitamin contents and caloric values of all the usual food stuffs. A wealth of details can be found in the two chapters devoted to contracted pelves.

The index is inadequate. No reference can be found in it to undue prolongation of pregnancy, the overcarried infant, induction of labor, episiotomy, birth injuries, etc. Obviously this is but a minor shortcoming which could be easily corrected in a subsequent edition.

—Hugo Ehrenfest.

In view of the widespread and increasing interest in the preservation of fetal and neonatal life, this book *Fetal and Neonatal Deaths* by Potter and Adair is timely. Those who are interested in attempting to salvage what is possible of the potential population loss will find much to aid them in their efforts.

The subject matter is divided into five chapters: The first chapter presents a statistical résumé of the present loss of life by stillbirths and neonatal deaths, followed by the physical characteristics of the normal fetus and infant. The technique of the fact finding by post-mortem examination is quite detailed. It is to be hoped that many hospital pathologists may note this section. There is an excellent discussion of anoxemia as a cause of death. Under special pathology, the specific lesions of the various organs and systems are discussed in relation to the manner in which they may cause fetal and neonatal deaths.

It is to be hoped that this book may become a working manual in every maternity hospital and that the general hospital pathologist may inform himself from it as to the exacting technique necessary in determining at autopsy the cause of death in the fetal or neonatal period.

—Philip F. Williams.

Leon's *Radiology in Obstetrics*⁹ was a presentation officially designated as the subject in 1939 before the Buenos Aires Obstetric and Gynecologic Society. It is a pamphlet of but eighty-seven pages, faultlessly gotten up, with excellent reproductions of x-ray plates. The subjects cover practically every phase briefly but clearly. The use of x-ray for the pregnant mother in order to determine the kidney and intestinal conditions, fetal conditions from the fourth month, determination of presentation, multiple pregnancy, monsters, intrauterine death and extrauterine pregnancy are all discussed. The amount of information contained in such short compass is amazing.

—R. T. Frank.

⁷*Obstetrical Practice*. By Alfred C. Beck, Professor of Obstetrics and Gynecology, Long Island College of Medicine, Brooklyn, etc. Second edition, 858 pages, 1043 illustrations. Williams & Wilkins Company, Baltimore, 1939.

⁸*Fetal and Neonatal Death*. By Edith L. Potter, M.D., and Fred L. Adair, M.D. University of Chicago Press, Chicago, Ill.

⁹*La Radiología en Obstetricia*. Estado Actual de sus Aplicaciones Practicas. By Juan Leon, Professor Adjunto de Clínica Obstétrica de la Facultad de Ciencias Médicas de Buenos Aires. Editor "El Ateneo," Buenos Aires.

This instrument is built into a compact carrying case and the loud speaker of the electrodynamic type is located in the detachable cover.

The microphone is of the crystal type and separated from the abdominal wall by a bell of soft rubber which "seals" itself to the tissue located over the most favorable fetal heart tone area. After the sounds are changed into electrical impulses, they are conducted through a four stage vacuum tube amplifier, with a gain of 120 decibels, to the cutting head which is of a permanent magnetic type. The pickup is of the crystal type. The input impedance matches the crystal microphone.

The recording is at a rate of 78 revolutions per minute and the discs are composed of a substance with an acetate base on an aluminum plate and can be audited many times without injury. Comments are recorded on the record.

A loud speaker or stethophones are used to assist in selecting the area in which the heart tones are most suitable for recording.

For reproduction, which can take place as soon as the recording is finished, a three-stage amplifier with a gain of 70 decibels is placed between the pickup and the loud speaker. The frequency response ranges from 50 to 8,000 cycles per second. The low or high frequencies can be selected at the will of the operator. The records can be reproduced on any phonograph.

NUMBER OF PATIENTS AND AGE OF FETUSES

On 58 pregnant mothers stethograms and disc recordings of the fetal heart sounds were made. In 52 of these cases the results were successful and both stethograms and cardiophonograms were completed and preserved. But with experience acquired in the first 36 cases, we have been able to record the fetal heart sounds in each case since then, that is, the last 22 cases.

In the six cases in which recordings were unsuccessful, in one the fetus was five and one-half months and the other five were between seven and one-half and eight and one-half months. In all these, the heart sounds could not be heard by aid of the stethoscope, the electric stethoscope or the loud speaker. In each case the mother has since been delivered of a normal child whose heart is normal in every respect. As to the position of the fetuses (no twins), 56 were vertex presentations and two were breech.

In five cases the attempt to record the fetal hearts resulted in failure but at later periods the recordings were entirely successful.

In the successful recordings the period of pregnancy varied from five months to three days before delivery. Three disc recordings were made during delivery and several other fetal heart sounds were broadcast before and during delivery but are not included in this series.

PATTERN OF FETAL HEART SOUNDS

The fetal heart sounds are definitely not of the ticktack type, but are as individual as those developed in the adult organ. Either sound may be accentuated but, contrary to past teachings, the second sound in a majority of cases is of greater intensity. In 28 cases the second sound is definitely of greater intensity (louder) than the first; in 8 cases the first sound is accentuated and in 16 cases the two sounds, varying somewhat, are of about equal intensity. The first sound is usually of longer duration and consists of more vibrations (three to eight cycles) though of lower frequency. The first sound may be very wide at times, and this is due to the separation of the auricular sound from ventricular part of the first sound. It is fairly well established that the first sound is composed of an auricular element which follows the auricular systole,^{13, 14} and the ventricular element which is either of valvular^{15, 16} or of valvular and muscular^{17, 18} origin. In Fig. 6 when the heart slows the auricular third sound (*a*) can be seen to appear before the principal vibrations of the first sound. This, of course, if still considered to be part of the first sound, would greatly increase its duration.

The frequency composition of fetal heart sounds is similar to that of adult heart tones. The sound energy is usually considerably less but at times the in-

This small monograph on *The Estimation of Pelvic Capacity*¹³ by Dr. Thoms recapitulates the methods which may be employed in ascertaining the capacity of the pelvis in the living subject, and discusses the findings resulting from such investigation. Roentgenometric technique is presented in detail and the clinical application of the findings is fully discussed. While much of the material in this recapitulation of the problem has already appeared, the monograph should be extremely useful to all obstetricians.

—Philip F. Williams.

Into this small volume, *Synopsis of Obstetrics*,¹⁴ Litzenberg, by omitting all theoretic and controversial data, has packed a great deal of useful knowledge. The text marked by clarity and brevity describes the normal reproductive cycle, then the abnormal conditions of the pelvis, passenger, and mother. While the discussion of operative obstetrics is short, it is definite as to indication and technique. The complications of the puerperium are discussed, including both immediate injuries and late sequelae.

Such a book should be of use to the student in review and as a pocket manual for the practitioner. Possibly an additional chapter or two on the premature child and the early complications of neonatal life might have been added.

—Philip F. Williams.

In the second edition of his *Die Geburtshilflichen Operationen*¹⁵ Martius has presented a beautiful atlas of operative obstetrics. The 281 illustrations explain pictorially practically all types of operations used in connection with operative deliveries. The text is short and each small paragraph emphasizes some point in the technique pictured. The physics of normal and abnormal labors are explained in the opening chapters. A note of marked value is found in the discussion of the operations which may be practiced in the home and those for which hospital surroundings are necessary.

—Philip F. Williams.

Congenital Malformations,¹⁶ by Douglas P. Murphy, a study of parental characteristics, with special reference to the reproductive process, is a short monograph, the data for which were obtained by a scrutiny of the birth and death records of Philadelphia, and a house-to-house investigation of the malformed individuals. It is a basic study which, though it does not elucidate the actual causes of malformation, contains important facts.

Malformations are more common among siblings and are prone to be identical in a family. Mating has been classified as efficient and inefficient, and is divided into various degrees. In Philadelphia, 1 in 213 live births showed malformations, and 25 per cent of malformed newborn were stillbirths. The rate among whites was twice as great as among negroes. Twenty-five per cent more malformations occurred in families in which a previous malformation had occurred. It appears that older mothers were more likely to give birth to malformed individuals, and this likewise applied to children born late in a family. Polyhydramnios and abnormal fetal movements had been noted in many cases. If two or more malformations occurred in the same family, 50 per cent were found identical. Of the malformed infants, 90 per cent were either stillborn or died within the first year. The influences producing malformations definitely were those in the germic cell

¹³*The Estimation of Pelvic Capacity.* By Herbert Thoms, M.D. Associate Professor of Obstetrics and Gynecology, School of Medicine, Yale University. The American Journal of Surgery, New York, 1940.

¹⁴*Synopsis of Obstetrics.* By Jennings C. Litzenberg, M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Minn. 157 illustrations, 5 in color, 376 pages. The C. V. Mosby Company, St. Louis, Mo., 1940.

¹⁵*Die Geburtshilflichen Operationen.* Ihre Ausführung und Anwendung. Von Prof. Dr. Med. Heinrich Martius. Zweite, verbesserte Auflage, mit 281, zum Teil farbigen Abbildungen. Georg Thieme, Leipzig, 1940.

¹⁶*Congenital Malformations.* By Douglas P. Murphy, Assistant Professor of Obstetrics and Research Associate in Gynecologic Hospital Institute of Gynecologic Research, University of Pennsylvania. University of Pennsylvania Press, Philadelphia, 1940.

prior to fertilization. The diet of many mothers who gave birth to malformed children was found defective in calcium, phosphorus, iron, and vitamins. This is an important contribution.

—R. T. Frank.

Laforet's monograph on the *Early Diagnosis of Pregnancy*¹⁷ takes up the historical aspects and the clinical signs. The main portion, however, is devoted to the biologic tests for pregnancy, particularly the Aschheim-Zondek test.

The monograph contains a large bibliography, a good synopsis of the situation, but no new contribution of any kind.

—R. T. Frank.

This monograph¹⁸ deals with the statistics on Italian mothers who have borne at least seven live children. It was found that the onset of their menarche was normal, that the climax occurred late, and hence their period of sex activity was prolonged. Various other observations dealing with the subject are contained in the many tables of this monograph which is based on the population of all portions of Italy.

—R. T. Frank.

In his monograph, *Grundlagen der Schwangerenernaehrung*¹⁹ Gaehtgens discusses the significance of present world-wide studies on nutrition. Regarding pregnancy as a nutritional problem, he brings out reasons for the exact determination of caloric intake in various energy-producing and protective foods. The metabolism of reproduction and the development of the fetus afford an opportunity to bring out the necessity for careful selection of the various food elements, whose chemical and physical qualities are described at length. Under the vitamins he discusses not only the outstanding deficiencies but also relative conditions which lead to the sub-clinical deficiency states. He describes laboratory tests for the determination of vitamin deficiencies.

There is an excellent chapter on the relationship of nutrition and lactation. The practical aspect of the subject is stated clearly with a consideration of how the pregnant woman can be educated to the need for the properly assorted diet, and how she can purchase it on a limited income. Gaehtgens feels that a good supportive diet can be purchased for 30 R.M. per month, which at the present rate of exchange will be \$12 in American money. According to a recent local government publication this sum would allow a wide range of values in an American family. Gaehtgens has appended a very complete bibliography, a number of appendices summarizing vitamins, their artificial substitutes, food values. A week's diet for a pregnant woman is detailed as to values and protective substances. The monograph is an excellent presentation of a much neglected subject.

—Philip F. Williams.

*Pictorial Midwifery*²⁰ by Sir Comyns Berkeley carries the sub-title *An Atlas of Midwifery for Pupil Midwives*. Though specifically designed "for pupil midwives preparing for the state examination," this small volume might prove, in the reviewer's estimation, also of considerable practical value to the medical student. While containing but few illustrations which could not be found in every standard textbook of obstetrics, this atlas is characterized by detailed description of each illustration in the appended legend. These legends represent the entire text matter and cover all important features in the anatomy, physiology and pathology of pregnancy, labor, and the puerperium. The drawings are well done and in each instance clearly present the particular points to be shown.

—Hugo Ehrenfest.

¹⁷*El Diagnostico Precoz Del Embarazo*. Par Dr. Carlos Colmeiro Laforet. 244 pages, illustrated. Libreria "Gali," Santiago de Compostela, 1940.

¹⁸*Il Ciclo Sessuale delle Madri delle Famiglie Numerose*. A cura di Corrado Gini e Pia de Orchi. Comitato Italiano per lo studio dei Problemi della Popolazione, Roma, 1939.

¹⁹*Grundlagen der Schwangerschaften-Ernaehrung*. Von Dr. Med. G. Gaehtgens. Universitaets Frauenklinik zu Leipzig. 142 seiten mit 9 abbildungen. Verlag von Theodor Steinkopff, Dresden, 1940.

²⁰*Pictorial Midwifery*. By Sir Comyns Berkeley, Chairman of the Central Midwives Board, Consulting Obstetric and Gynecological Surgeon to the Middlesex Hospital, etc. Third edition, 166 pages. Williams & Wilkins Company, Baltimore, 1939.

As childbearing is a natural process, pregnancy should be a healthy, happy time. Thus states the author in his preface in *Expectant Motherhood*²¹ and proceeds to show in subsequent pages how this may be achieved. He answers well the "whys" and the "wherefores" which intelligent women are desirous of being informed about, and this is done in an effort to supplement rather than confuse the doctor's instructions. The contents of the book very completely and satisfactorily cover the accepted facts of the prenatal period, of labor, and of the puerperium, although one may question the value of the somewhat technical descriptions in the chapter on growth and development. Chromosomes and trophoblast are still outside the domain of appreciation by the laity. The comparative descriptions of various "painless labor" procedures may lead to a personal selection of method and consequent dictation to the doctor. However, the book as a whole is a very serviceable addition to the many books on the subject which are finding deserved circulation among the intelligent laity. It will undoubtedly explain many things which should be known to our prospective mothers.

—George W. Kosmak.

Miscellaneous

It is an esthetic pleasure to study the *Atlas of Surgical Operations*²² by Cutler and Zollinger, which is beautifully illustrated by Mildred B. Coddington. The authors present this as "a book about surgical craft." It is designed to supply the intimate technical steps of surgical operations; "... to bring forward to the unfledged surgeon in a single small volume the simpler and standardized procedure of modern surgical practice." These aims have been excellently attained.

After a very short introduction, the atlas is arranged so that on one page appears the text, which is extremely short but adequate; upon the other page, the illustrations of the operative procedure in various steps.

The entire subject of general abdominal surgery is covered, and in addition, gynecologic operations, including vaginal plastics, infections of the hands, sutures of the nerves and tendons, the treatment of varicose veins, periarterial sympathectomy, and amputations are shown in eighty-four plates.

The illustrations deserve special commendation. They are line drawings, exceptionally clear, delicate and true to nature without exaggeration, every step being clearly indicated. I welcome this departure from the current half-tone which so readily covers many sins of inaccuracy and of poor drawing.

The authors have shown excellent judgment in their selection of material and types of operation. It would of course be possible to differ here and there with the value of the techniques employed but on the whole, no more comprehensive and readily understandable book on surgical technique has appeared in many years. This book should enjoy a wide popularity.

—R. T. Frank.

*Specialties in Medical Practice*²³ under the editorship of Edgar van Nuys-Allen appears in loose-leaf form in two volumes, by numerous authors. This work is intended to be a ready source of information to all who practice medicine, and is meant particularly for the specialist who may desire to inform himself about other specialties. It is likewise meant for the medical student.

Volume I contains seven chapters covering ophthalmology; diseases of the ear, nose, and throat; neurology; psychiatry; the vitamins and vitamin deficiency diseases; allergy; and orthopedic surgery.

²¹*Expectant Motherhood*. By Nicholson J. Eastman, M.D., Professor of Obstetrics in Johns Hopkins University and Obstetrician-in-Chief to the Johns Hopkins Hospital. Little, Brown & Co., Boston, 1940.

²²*Atlas of Surgical Operations*. By Elliott C. Cutler, Moseley Professor of Surgery, Harvard University, etc., and Robert Zollinger, Assistant Professor of Surgery, Harvard University, etc. Illustrated by Mildred B. Coddington, 179 pages. The Macmillan Company, New York, 1939.

²³*Specialties in Medical Practice*. Edited by Edgar van Nuys-Allen, Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, Minn., etc., with a Foreword by Donald C. Balfour, Consultant in Surgery, the Mayo Clinic. Loose-Leaf, in two volumes, illustrated. Thomas Nelson and Sons, New York, 1940.

In the second volume are taken up obstetrics and gynecology; endocrinology; urology; proctology. Dermatology and syphilology are in preparation. The endocrine aspects of the ovary are not included under endocrinology, as they have been dealt with to some extent under obstetrics and gynecology.

This publication has the advantage of its loose-leaf format with the possibility of keeping it constantly up to date.

—R. T. Frank.

The Bodanskys, Meyer and Oscar, have produced a general treatise of medicine, *Biochemistry of Disease*,²⁴ viewed from the angle of biochemistry. Within its 684 pages, the relation of biochemistry to the understanding of the pathogenesis, the course and the treatment of disease is shown in a clear, sequential and understandable fashion. This very difficult achievement has been accomplished by leaving out many elementary discussions and details of laboratory technique, and by arranging the material according to clinical entities. Nevertheless, innumerable of the current and constantly used procedures are given in sufficient detail to be readily followed by the clinician.

The subjects have been covered in 18 chapters which include diseases of blood, heart, respiratory, kidney and urinary tracts; the digestive tracts, the liver and biliary systems also are dealt with. The chapter on endocrinology includes pancreas, adrenals, pituitary, thyroid parathyroid, and male and female gonads. The diseases of bone, muscle, disorders of nutrition and of metabolism are taken up. The final chapter includes neurologic and psychiatric disorders.

It is surprising how this immense amount of material has been incorporated in one volume in such a clear-cut and readily understandable fashion. The bibliographies at the end of the chapters also make the book of value for reference.

Any physician or surgeon who is interested in following the steady advances of biochemistry, will find this book of utmost importance to him, either for referring to individual facts or by gradual rereading the individual chapters to clarify his knowledge, and to enable him to understand what biochemical laboratory tests really signify.

—R. T. Frank.

Biological Symposia,²⁵ edited by Jaques Cattell, was conceived to celebrate the one hundredth anniversary of the cell theory attributed² to Schleiden and Schwann. The monograph covers the cell theory, mating types, and their mating action in the ciliate infusoria and their chromosome structure, written by numerous well-known workers in this field. These articles plainly show that Schleiden and Schwann have received too much credit, as many predecessors whose work dates back for more than two hundred years had laid the foundation stones upon which the cell theory was actually based. Moreover, the intervening century has demonstrated that, as originally conceived, this theory requires many modifications. Nevertheless, the popularization of the cell concept must be credited with having speeded up the work immeasurably. The articles make most interesting reading both for the profession and for the laity.

—R. T. Frank.

The eighth edition of Jordan's *Textbook of Histology*²⁶ has appeared. This standard textbook has slowly developed and crystallized since it first was published in 1916. In the present edition, the chapters on muscle, endocrine organs, the female reproductive system, and the blood vascular system have undergone particularly thorough revision. The author has wisely dropped the chapter on histologic technique and directions for laboratory work.

This is an adequate textbook, very well illustrated, with illustrations drawn from standard sources, and some of the illustrations in colors. Another improvement is

²⁴*Biochemistry of Disease*. By Meyer Bodansky, M.D., and Oscar Bodansky, M.D. 684 pages. The Macmillan Company, New York, 1940.

²⁵*Biological Symposia*. Edited by Jaques Cattell, Editor of *The American Naturalist* and *American Men of Science*. 238 pages, illustrated. The Jaques Cattell Press, Lancaster, Pa., 1940.

²⁶*A Textbook of Histology*. By Harvey Ernest Jordan, Professor of Anatomy and Director of Anatomical Laboratories, University of Virginia. Eighth edition, 690 pages, 609 illustrations. D. Appleton-Century Co., Inc., New York, 1940.

a bibliography which concludes the volume, because this book is not only used by medical students, but is of utmost value to physicians in looking up the fundamental morphology. The concept of the endocrine glands is somewhat loosely drawn as many will still take exception to including the carotid and coccygeal glands among the endocrine organs, and would prefer to have the pancreas as well as the male and female gonads more closely associated with the endocrines. Each edition has seen improvement in this work which is always kept fully up to date.

—R. T. Frank.

The first Chilean Surgical Congress²⁷ was held in 1939. Its proceedings are contained in a large, handsome volume of 565 pages. The three themes officially assigned were acute pancreatitis, treatment of uterine fibroids (surgical, radiotherapeutic, as well as experimental, the latter based on the fundamental observations of Nelson made in 1937), and fractures of the neck of the femur. In addition, a series of articles covering various surgical and gynecologic-obstetric subjects were reported. The participants in this activity were mainly from Chile and Argentina although other South American states were represented. The articles are profusely and well illustrated.

—R. T. Frank.

In this sixth edition of *The Art of Anesthesia*,²⁸ Dr. Flagg has inserted a great deal of new material. A prominent suggestion contained in the present volume is in regard to those who are skilled in anesthesia becoming the leaders in the movement to provide promptly available services to meet the existing asphyxial mortality of the 1,000 deaths a week in the United States, and that such an organization be the leaders in directing resuscitation teams.

There is a critical review of the latest views relating to the agents commonly employed as basal anesthetics. This section should be of interest in the consideration of the various methods of relieving pain in labor which are commonly employed.

Flagg states in regard to chloroform that it should cease to be used as an anesthetic in obstetrics and regards gas-oxygen as valuable only as an analgesic in obstetrics. He says that full-term babies in utero are more susceptible to ethylene gas than their mothers; therefore, the gas is not safe for operative obstetrics.

There is an excellent chapter on the postoperative nursing of the patient who has had various types of inhalation anesthesia. For the benefit of students, as well as anesthetists, he has provided a new chapter on preanesthetic physical examinations.

Obstetric anesthesia forms the subject of a well-thought-out section. In connection with the suggestion that anesthetists direct resuscitation efforts, the chapter on artificial respiration has been entirely rewritten. In the chapter on the causes of deaths in anesthesia, Flagg presents a very concise discussion of asphyxia of the newborn and its treatment. The subject matter is comprehensive and the book should be in the armamentarium of all anesthesia departments.

—Philip F. Williams.

The National Organization for Public Health Nursing offers for the third time, a *Manual of Public Health Nursing*²⁹ to suggest procedure, which may serve as a guide to the public health nurse in the field. This may be applied to the small community, county, large city services or state. As the scope of public health nursing in recent years has increased under governmental and allied agencies, the need for an up-to-date manual is apparent.

In the first part of the book, administration and organizations are thoroughly discussed in reference to the relationship of public health nursing to other services, the nurse's work and education. The education of the family as to health is thoroughly detailed.

²⁷Primer Congreso Chileno y Americano de Cirurgia. Imprenta Universitaria. Santiago de Chile, 1939.

²⁸The Art of Anesthesia. By Paluel J. Flagg, M.D., Visiting Anaesthetist to Manhattan Eye and Ear Hospital, etc., New York. Sixth edition, revised. With 161 illustrations, 491 pages. J. B. Lippincott Co., Philadelphia, 1939.

²⁹Manual of Public Health Nursing. Prepared by the National Organization for Public Health Nursing. Third edition, 529 pages. The Macmillan Company, New York, 1939.

More specific and detailed services which the nurse may be called upon to carry out are given in Part III. The section on maternity services is a complete manual on obstetric nursing whether it be in rural areas or congested city districts. The directions are clearly and concisely given. The nurse is expressly directed as to her duties in regard to the physicians and hospital services. The technique recommended is above reproach. A new and pertinent section deals with recent public health work in the control of venereal diseases.

This is an excellent book. The directions are concise, material is wisely written, and the book is warmly recommended not only to public health nurses but to those who direct the activities of such women.

—Philip F. Williams.

This volume on *Sexual Pathology*³⁰ by the late Magnus Hirschfeld has been condensed from the original three-volume edition. In it Hirschfeld has divided the subject matter into three main divisions: sexual symbolism, hypereroticism, and impotence.

In the section devoted to Sexual Symbolism he details the nature of the various abnormal attractions, both masculine and feminine. Under Hypereroticism he discusses the quantitative variations of the sexual urge and its various types of output, including murder. Under the section on Impotence there is a general discussion of potency and fertility with case histories relating to the various types of impotence and frigidity in both male and female. Hirschfeld offers few, if any, suggestions as to the therapeutics of these abnormal ideas, practices, or conditions, which is to be regretted, since the treatment of these aberrations of the sexual instinct is difficult.

—Philip F. Williams.

This volume on *Sex in Marriage*³¹ by Groves and Groves is a clear and common sense presentation of many of the problems which affect marriage. The long clinical experience of the authors, dealing in family problems, has eminently fitted them to write this book. The problems of sexual adjustments are described with an understanding philosophy which should make the book valuable to many individuals. A very practical chapter on birth control answers many questions often asked by anxious couples. To those whose practice includes discussion of family problems, particularly regarding marriage, this book may be highly recommended.

—Philip F. Williams.

*Sex in Life*³² by Eugen Steinach is a translation from the German. It is really a popular scientific account of all of Steinach's researches which he was motivated to write in order to clarify misunderstandings and misstatements. It is likewise an autobiography of this now seventy-nine-year-old scientist. The book is interestingly written, and in the main, focuses upon Steinach's own contributions, although some credit is given to others.

The translation is excellent. The experiments based upon physical and psychical investigations to determine the causes of erotization are described in detail. Transplantation experiments, first of the testicle (begun in 1884) and later of the ovary, with re-establishment of sexual potency, as well as the well-known feminization and masculinization experiments, are recounted. The less well-authenticated transplantation on the human are described by the author, as well as rejuvenation by vasoligation and the production of experimental hermaphroditism. Finally sex hormone therapy is referred to. This book is very personal, very well written, somewhat boastful, but informative.

—R. T. Frank.

³⁰*Sexual Pathology*. By Magnus Hirschfeld, M.D. Authorized Translation by Jerome Gibbs. Originally published in three volumes. 368 pages. Emerson Books, Inc., New York, 1940.

³¹*Sex in Marriage*. By Ernest R. Groves, Professor of Sociology, University of North Carolina and Gladys H. Groves, Director of the Marriage and Family Council, Inc., Chapel Hill, North Carolina. Emerson Books, Inc., New York, 1940.

³²*Sex and Life*. Forty Years of Biological and Medical Experiments. By Eugen Steinach, M.D., Ph.D., formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by Josef Loebel, M.D. 252 pages. The Viking Press, New York, 1940.

Kehrer's monograph on the *Psychical Diseases of the Menopause*,³³ from its clinical aspects, discusses the many mental changes which can be found at this stage of life, particularly menopausal melancholia and senile dementia. The monograph is difficult to read because of lack of adequate arrangement.

—R. T. Frank.

The useful and widely appreciated *Medical Dictionary*³⁴ by Stedman has appeared in a new (fourteenth) and extensively revised edition. Steady progress, especially in the fields of endocrinology and in biochemic investigations, has necessitated the inclusion of many new terms and names. However, a further increase in the bulk of the volume was prevented by the elimination of some of the older illustrations.

During preparation of this edition, Dr. Stedman died, at the age of eighty-four, and the work was finished by his nephew and former collaborator, Dr. Stanley Thomas Garber, who is now taking over the responsible task of editing future editions of this volume indispensable to the physician's library.

—Hugo Ehrenfest.

Two books^{35, 36} by the same author may prove amazing examples of the formation of a new cult such as was based on the Abraham's apparatus a number of years ago, and which enjoyed a passing vogue. The author appears to be an extremely well-informed individual who follows the literature most minutely. His hypotheses and theories are too fantastic to deserve serious review. The entire subject matter is based upon an instrument called the Zykloskop which, in the first volume designed for the laity and called the Cycle of a Woman, Reform of Marriage, is designed to be a sort of a home guide. According to the author, by means of the reduction time determined by this modification of the spectroscope, ovulation can be readily determined and the so-called safe period thus definitely ascertained. By this same means, early pregnancy is supposed to be determined. It is a well-gotten-up monograph with excellent illustrations taken from standard sources (to whom no credit is given).

The second book is *Endogenous Endocrine Therapy in Gynecology*³⁶ in which a fantastic description of the cure of cancer, even with metastases, is said to have been obtained by means of stimulation of the pituitary with short wave radiation. This treatment is supposed to step up the function of the various endocrine glands and stimulate their activity, with resultant disappearance of the malignancies.

In the present disturbed world situation, I have no means of finding out what type of reception the theories of the author have been accorded in his own home, that is Holland. Doubtless in this country, cranks or charlatans will grasp at this type of diagnosis and treatment with avidity.

—R. T. Frank.

Scudder brings a recapitulation of his clinical and experimental research work on shock to the profession in this monograph *Shock: Blood Studies as a Guide to Therapy*.³⁷ After reviewing the nature of shock, discussing its similarity with certain phases of Asiatic cholera, and the evidence of his experiments and clinical research, he offers an evaluation of the various methods of treating shock which are in use today. He describes certain physical-chemical tests which, showing changes in hemoconcentration, are able to be used in a prognostic manner to bring earlier and more effective treatment in an early stage of shock. In the discussion regarding the changes in potassium in shock, he concludes that one of the variables

³³*Die Krankhaften Psychischen Störungen der Rueckwandlungs-Jahre.* Von Professor Dr. Ferdinand Kehrer, Psychiatrische und Nerven-Klinik, Universitaet in Muenster. Verlag von Julius Springer, Berlin, 1939.

³⁴*Practical Medical Dictionary.* By Thomas Lathrop Stedman, M.D., and Stanley Thomas Garber, M.D. Fourteenth, revised edition, with etymologic and orthographic rules. Illustrated, 1303 pages. Williams & Wilkins Company, Baltimore, 1939.

³⁵*Der Zyklus der Frau. Reform des Ehelebens.* Von Dr. Jules Samuels, Amsterdam. G. Naef, The Hague, 1938.

³⁶*Endogene Endokrinotherapie in der Gynaekologie.* Von Jules Samuels, Chirurg-Frauenarzt, Amsterdam. A. W. Sijthoff's Uitgeversmaatschappij, Leiden, Holland, 1938.

³⁷*Shock: Blood Studies as a Guide to Therapy.* By John Scudder, M.D., Med. Sc. D., F.A.C.S. 235 pages and 55 illustrations, 5 plates. J. B. Lippincott Company, Philadelphia, Montreal, London, 1940.

produced by certain factors is an alteration in potassium metabolism, a derangement which serves as an indication of profound cell injury. He discusses the physical measures of hemoconcentration, and proceeds to evaluate them in experimental shock and shock due to other causes. He outlines the treatment employed in various types of shock and the results. He states finally that all factors which tend to maintain a normal ratio between the extracellular sodium and intracellular potassium are beneficial in the treatment of shock as they tend to favor normal action currents.

A laboratory manual is appended which discusses in detail the methods employed in studying hemoconcentration. There is a bibliography of some 500 references to the subject. This presentation should be of marked interest not only to the pathologist, but to the clinician in the treatment of shock.

—Philip F. Williams.

Dr. Robbins reviews the use of *Cyclopropane Anesthesia*³⁸ in this monograph. He discusses the physical and chemical properties of the agent, its effects upon the various systems and tissues, and proceeds with an exposition of the clinical administration of this gas. The complications and indications and contraindications are well set forth. Nor has he neglected to discuss the hazards in a chapter on explosions.

The book represents, too, a review of some 200 articles bearing on the subject, and the experiences which have been narrated in the use of the gas in some quarter million anesthetics. Particularly, and to the interest of the obstetrician, he brings out the relationship of the gas as an anesthetic in pregnancy to the elevated cardiac output. There is an excellent discussion of the relation of this anesthetic agent, and various types of sedation used in labor, to asphyxia of the newborn. The author feels that full surgical anesthesia with this agent can be produced in the mother without any interruption of fetal respiration.

It is particularly interesting to note his conclusions on page 129, in regard to anesthesia necessary in toxemia of pregnancy. He states that cyclopropane anesthesia produced no liver damage detectable by the bromosulphthalein test and that the kidneys show less disturbance after cyclopropane than after ether, and that the contractions of the gravid uterus are not altered by cyclopropane.

From a review of the literature one might conclude that preoperative medication is not necessary in operative obstetrics conducted with cyclopropane. It is mentioned that in a reported series of 400 cesarean sections under different agents, in 94 performed with cyclopropane there was less need for resuscitation measures and less evidence of postoperative gas pains. This book merits careful reading not only by the anesthetist but also by the clinician who must also judge what anesthetic his patient may need.

—Philip F. Williams.

Lewis and Hopper present a beautifully prepared monograph on *Medical Mycology*.³⁹ The material developed during a ten-year post-graduate course in dermatology, fortified by laboratory and clinical background. The illustrations are profuse and thoroughly correlative. The book is divided into two parts: The first dealing with the clinical, theoretic, and experimental aspects; and the second part concerning the laboratory methods. The first part presents a review of the various mycoses and fungus diseases in regard to diagnosis and treatment. The second part presents a detailed account of the technique of the various laboratory studies necessary in mycotic diseases. The book is thoroughly documented.

—Philip F. Williams.

³⁸*Cyclopropane Anesthesia*. By Benjamin H. Robbins, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. The Williams and Wilkins Company, Baltimore, 1940.

³⁹*An Introduction to Medical Mycology*. By George M. Lewis, M.D., Associate, and Assistant Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University, and Mary E. Hopper, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. The Year Book Publishers, Inc., Chicago, Ill., 1939.

In this book, *Synopsis of Operative Surgery*,⁴⁰ Mobley gives a concise description of the technique of the more common surgical procedures. The fundamentals of anesthesia, postoperative care, and general considerations of surgical technique, hemorrhage, shock, drainage, and other pertinent topics are briefly, yet clearly, presented.

An excellent compendium for review, a well-illustrated guide for technique.

—Philip F. Williams.

This brochure, *Youth Looks at Cancer*,⁴¹ is offered by the Westchester Cancer Committee of the American Society for the Control of Cancer, as a part of a general effort to educate the public in regard to this disease. The leaders of this Committee feel that through the use of the educational efforts depicted, such as field and laboratory work, motion picture films and technical exhibits, young people may be interested in the biologic aspects of the subject at an age when emphasis may be rendered without accompanying fright. To those who are interested in the campaign against cancer through education of the laity, this booklet should provide much valuable information.

—Philip F. Williams.

⁴⁰*Synopsis of Operative Surgery*. By H. E. Mobley, M.D., F.A.C.S. Chief of Surgery at St. Anthony's Hospital, Morrilton, Arkansas. 360 pages, 339 illustrations, 39 colored illustrations. The C. V. Mosby Company, St. Louis, Mo., 1940.

⁴¹*Youth Looks at Cancer*. The Westchester Cancer Committee. Brookville Press, Inc., Brookville, N. Y., 1940.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Endocrinology

Hamblen, E. C.: Clinical Correlates of Functional Uterine Bleeding, *South M. J.* 32: 308, 1939.

While there is a tendency for the incidence of bleeding irregularities to "peak" during adolescence and the climacteric, an association of these with puerperal recovery and also with surgical and roentgenotherapeutic procedures results in a more even distribution of frequency among the different age groups. There is a strikingly low incidence among colored women. No general correlations exist between menarchal and menopausal ages and irregularities of bleeding. Parity apparently predisposes to their development. Fertility is lowered definitely by their existence.

The subjective symptomatology of patients with irregularities of flowing is varied: obesity and headache are common symptoms; dysmenorrhea is relatively infrequent. Gynecologic abnormalities and disease are encountered frequently in these patients.

In over 50 per cent there are one or more physical signs suggestive of endocrine disease. The greater portion of these signs is related to lowered function of the thyroid or of the ovaries. Little roentgenologic evidence of pituitary disease is encountered.

Most functional bleeding occurs from estrogenic endometriums, although any type of irregular bleeding may be associated with any of the normal or abnormal endometrial patterns. Excessively proliferated estrogenic endometriums occur most frequently in conjunction with climacteric menometrorrhagia. Various degrees of progestational proliferation are encountered commonly in the endometriums of patients having less severe irregularities. There are no irregularities which are peculiarly characteristic of the classical sex endocrine syndromes, except for that of hypo-ovarianism, in which amenorrhea and oligomenorrhea are common. Studies of the metabolism of progesterone in various types of irregularities by determinations of sodium pregnanediol glucuronide have indicated that the endometrial pattern from which bleeding occurs cannot be used reliably as an indicator of the functional level of the corpus luteum.

J. P. GREENHILL

Mocquot, P., and Palmer, R.: The Temperature Curve and Hormonal Actions in Gynecology, *Presse méd.* 48: 305, 1940.

The authors maintain that the interrelating anatomic and physiologic phenomena which constitute the genital cycle can be interpreted, aside from menstruation, by some clinical manifestations apparent in the normal state, but capable of attaining more pronounced patterns in pathologic situations. Variation of the thermal curve is one of these manifestations. It shows a more or less regular periodicity, duration, constancy, and chronologic uniformity with various incidents and accidents during the genital cycle. These recorded thermal variations are important adjuncts to the diagnostic armamentarium of the hormonal status. Thermal variations make easier the diagnosis, classification, and treatment of certain pathologic conditions.

tensity is, surprisingly, greater than the adult sounds (Fig. 6). However, the ear must operate close to the lower threshold of audibility and in extreme cases is incapable of detecting the sounds (9 in this series). Through the ordinary stethoscope, the acuity of hearing at low frequencies is obviously one essential requirement in obstetric auscultation, according to Williams and Dodge.¹⁹

FETAL RHYTHM AND RATE

The rhythm, as in the adult, is constantly changing but in all it seems to be of sinoauricular origin. The heart rate is variable and in some cases this is extreme, as in Fig. 6 it varies from 92 to 150. For the series of 52 the fetal heart rates range from 124 to 163. In two cases the first sound is reduplicated as shown in the stethogram (for example Fig. 7), but in the disc recordings, these give the impression of a presystolic gallop.

DURATION OF FETAL SYSTOLE AND DIASTOLE (VENTRICULAR)

The identification of diastole and systole is not as difficult as it seems, for diastole is nearly always the longer silence and the first sound is practically always wider than the second. By slowing the revolutions of the turntable when reproducing the recordings, the sounds and silences, due to the slow rate of reproduction, can be more easily analyzed.

It is difficult at times to know just where the systole begins, for as the auricular element of the first sound moves forward into the presystolic space it may separate from the first sound and become the presystolic third sound. If it is included in the duration of the systole, this greatly increases the duration of the systole graphically, even though the ventricular systolic contraction is really shorter.

The length of both systole and diastole is constantly changing though diastole is the more variable. As the heart rate decreases, both increase in duration, systole proportionately less than diastole. For example, in Fig. 6, when the fetal heart rate is 150 per minute, systole occupies 0.18 and diastole 0.23 second while, when the rate is 92, systole is 0.23 second in length and diastole is as great as 0.53 second (one complete cardiac cycle is 0.75 second and this is at a rate of 80 per minute).

In this series the systolic phase varies from 0.16 to 0.23 second, while the diastolic ranges from 0.17 to 0.53 second.

In one case (Fig. 3) diastole is shorter than systole; in two cases diastole and systole are equal, but in the rest of the series diastole is the longer of the two.

All measurements were made on stethograms which were exposed at a rate of 50 mm. per second, although in the illustrations the rates are always 25 mm. per second.

These measurements are not in agreement with those given by White²⁰ (number of heart rates measured and age not given), who states that in the human heart the duration of systole and diastole is approximately as follows:

At rate of 90 systole is 0.32 and diastole 0.34 second.

At rate of 100 systole is 0.30 and diastole 0.30 second.

At rate of 120 systole is 0.28 and diastole 0.22 second.

At rate of 150 systole is 0.23 and diastole 0.17 second.

In this series of 52 cases in only one fetus is the systole longer than diastole, and in this the heart rate is 163. All fetal heart rates, with two exceptions, are over 130 per minute, while one varies from 92 to 150.

Also these measurements do not agree with those given by Boone²¹ who finds, in children at the rate of 126, systole (0.24) and diastole (0.24) are equal; between 126 and 180 systole is always of greater duration and below 126 diastole is always of greater length. However, it must be stated he starts the measurement of systole in line with about the middle of the ascending limb of the R-wave in the electrocardiogram which is taken simultaneously with the stethogram.

tumor. Blood studies showed only a moderate increase in the amount of circulating estrin. The endometrium was that of a sexually mature adult, with prominent, dilated endometrial glands. An interesting feature of the chemical analysis of this tumor was that 40 per cent of the tumor was composed of lipoids. The authors feel that tumors associated with marked clinical signs of hormone production contain large quantities of lipoids. After removal of the tumor there was incomplete retrogression of the secondary sexual characteristics.

WILLIAM BERMAN

Baruk, David, Racine, and Mlle. Leuret: Folliculin Psychoses and Circulatory Disturbances (Experimental Study on the Action of Folliculin upon the Cerebral Circulation), Presse méd. 48: 281, 1940.

The authors review the role of hyperfolliculinism upon the psyche and discuss the varying degrees of mental changes occurring from the minor vasomotor manifestations to the more marked major psychoses.

Experimentally they exposed the cerebrums of rabbits and monkeys to direct observation by a method described by both Riser and Villaret and others. Both oily and water solutions of folliculin were used and both types produced the same response, although the response to the aqueous solution was more rapid.

They found that folliculin injection into the animals produces a distinct diffuse vasodilatation of the cerebral circulation effective upon both large and small vessels. The brain appears congested while the vessels seem turgid. Biopsy specimens of the brains reveal distinct increase in vascularity as opposed to specimens from control animals.

CLAIR E. FOLSOME

Maranon, Richet, Pergola and Lesueur: Secondary Tetany from Hyperfolliculinemia, Ann. d'endocrinol. 1: 142, 1939.

The authors are of the opinion that other endocrine influences, distinct from the parathyroid, can also be pathogenic in the development of the tetany syndrome. They cite 4 cases of tetany induced by excessive folliculin, two of them being males. Both of these males had a folliculinemia.

Case 2 was a young man of 20 years who had been operated upon at the age of 18 for the reduction of a bilateral cryptorchidism. There were found 800 I.U. of folliculin per 1000 c.c. of urine. He developed a latent tetany with paroxysmal crises. Marked relief followed testosterone propionate treatment.

Case 3 was a male of 49 years who had chronic and paroxysmal tetany. It was determined that there were 150 to 300 I.U. of folliculin per 1 liter in the urine. Testosterone treatment caused the tetany to disappear.

Both female patients presented a tetany. In Case 1 the patient experienced a severe and typical tetany crisis when folliculin was accidentally given intravenously. The patient in Case 4 secured marked relief from premenstrual tetany with the combined treatment of luteal and testicular hormones.

The authors believe the hypothesis best explaining this correlation is that excessive folliculin may directly modify the calcium metabolism by reducing parathyroid secretion.

CLAIR E. FOLSOME

Ramos, Alberto Peralta: The Quantitative Analysis of Folliculin as the Basis of Clinical and Therapeutic Orientation in Gynecology, Presse méd. 48: 270, 1940.

The author summarizes the known physiologic facts of folliculin and its interrelationships with other hormones. He believes that blood and urinary folliculin levels must be known to treat correctly the functional hemorrhages, and in particular those occurring in puberty and menopause.

Six elaborate charts are presented in the paper. In Charts 2 and 3 it is noted where the author indicates that folliculin is released to act directly upon the "sexual center of the diencephalon."

The writers advise that rectal temperatures be taken daily, at seven in the morning and five o'clock in the afternoon. The same clinical thermometer and the exact time of temperature taking are important as the variations of the thermal curve seldom exceed 2/10 to 4/10 of a degree. To establish the norm for each individual three months of temperature readings are adequate.

CLAIR E. FOLSOME

Turpin, Wm. R., Chassagne, P., and Lefebvre, J.: Prepubertal Megalothymia. A Planimetric Study of the Thymus During the Growth Period, Ann. d'endocrinol. 1: 358, 1939.

The authors using the recently developed planigraphic technique studied the thymus gland in 82 children, 35 boys and 47 girls. The children's ages varied from 2 to 15 years.

The writers state that the planigraphs obtained in the study demonstrate an increasing volume of the thymus during the growth period of the child. The maximal volume is reached at the time of puberty and warrants terming the clinical entity, as "prepubertal megalothymia." The maximal increase occurs later in boys than in girls and this difference is particularly striking in opposite sexed twins.

The prepubertal megalothymic shadows disappear one or two years following puberty.

The authors describe this new technique in excellent detail and the article is well illustrated with graphs, charts, and 10 photographs.

CLAIR E. FOLSOME

Westman, Axel: Differential Diagnostic Problem in Virilizing Diseases of Women, Acta obst. et gynec. Scandinav. 19: 455, 1939.

Westman reports three cases of pronounced symptoms of virilism. The first case was a marked Cushing type with very round face and considerable obesity of the breast and abdomen, while the extremities were thin. The patient also showed a strong growth of beard, numerous striae formations, increased blood pressure, and signs of marked osteoporosis. The ovaries were atrophic, and the patient was suffering from amenorrhea. X-ray treatment of the pituitary body led to a partial improvement.

The second case resembled the first, but striae formations and osteoporosis were not present. A large suprarenal adenoma was found on the right side and was extirpated. The third case presented a virile hirsute type. The patient had a deep bass voice. She suffered from amenorrhea, and a marked hypertrophy of the clitoris was present. The distribution of fat, on the other hand, was normal. No increase of blood pressure was present, nor changes in the skin. One of the ovaries was the seat of an arrhenoblastoma and one suprarenal was markedly enlarged. After the ovarian tumor had been removed, the growth of hair decreased, particularly in the face, and the menstruation became normal. The change in the voice remained, however, as did also the hypertrophy of the clitoris, and it is debatable whether this should not be considered to be due to an excessive functioning on the part of the enlarged suprarenal gland.

The cases illustrate the diagnostic difficulties in discovering the cause of virilism in women. Similar pictures of symptoms may be caused by tumor formations either of the pituitary body, the suprarenal glands, or the ovaries.

J. P. GREENHILL

Stabler, Frank, and Thomson, J. Greig: Granulosa-Cell Tumour with Precocious Sexual Development in a Child Aged Six, J. Obst. & Gynaec. Brit. Emp. 47: 199, 1940.

The authors report a case of a child aged six years and two months who developed signs of sexual precocity, followed by marked vaginal bleeding. Examination revealed an abdominal tumor which on laparotomy proved to be a left-sided ovarian cyst. On microscopic examination it was found to be a granulosa-cell

the psychic difficulty of this group was unusually improved. In all three cases of pubertal hemorrhages the results were excellent. In the 26 cases of adult women with dysmenorrhea only those with concomitant menorrhagias obtained the most direct results. No figures are given relative to this group. In 11 cases of sterility, on the basis of endocrine imbalance, 8 had primary sterility and but 1 became pregnant, while one of the 3 secondary sterility patients became pregnant.

In all 7 instances menopausal bleeding was easily controlled by gonadotropic hormone although 2 of these patients underwent subsequent laparotomy. The authors also treated 1 patient with eczema of the face and hands associated with hypoestration; 2 patients with habitual abortion; 3 patients with pruritus vulvae and 2 with menorrhagia on the basis of cystic ovaries. All of this latter group obtained partial or complete relief from their complaints.

The writers conclude that gonadotrophic hormone is an efficacious aid in the treatment of the female functional disorders.

CLAIR E. FOLSOME

Fluhmann, Frederic: *Biologic Characteristics of Equine Gonadotropic Hormone*, West. J. Surg. Obst. & Gynec. 48: 63, 1940.

The equine gonadotropic hormone was discovered in 1930 by Cole and Hart. It occurs in high concentration in the blood of pregnant mares but is present only in slight traces in the urine. The biologic characteristics of this hormone show many properties common to the other known gonadotropes, but it appears to be an entirely new entity. It probably is not a product of the hypophysis but another "pregnancy hormone."

The exact effect of this equine hormone on the human ovary is not definitely known. Davis and Koff claimed to have produced ovulation in 16 out of 36 women. But such effectiveness is doubted by others, by Hartman on the basis of extensive experiments on monkeys. Clinically, the hormone has been employed in the treatment of amenorrhea, sterility, metropathia hemorrhagica, etc. Some of the reported results are surprising, thus as Hall's who found that 24 out of 43 sterile women became pregnant following this treatment.

The author's clinical experience in 15 patients so far has not been at all encouraging. Further extensive observations will be required to determine the correct selection of cases, proper dosage, and most favorable time of administration.

HUGO EHRENFEST

Varangot, J.: *Endocrine Therapy of the Dysmenorrheas*, Presse méd. 48: 220, 1940.

The author used hormonal therapy in treating 27 cases of dysmenorrhea. Twenty of these patients were followed a sufficient time to permit conclusions. Nine of this latter group had primary dysmenorrhea.

Massive folliculin therapy gives satisfactory results in cases of dysmenorrhea due to uterine hypoplasia. The author has not had sufficient experience with testosterone to warrant an opinion of its efficacy. Last, progesterone gives excellent results in primary dysmenorrhea, if used in sufficiently large doses (20 to 25 mg. progesterone, 4 to 5 times, in the week preceding the period).

CLAIR E. FOLSOME

Dick, M., and Hooker, C. W.: *Absence of Acute Effects of Sex Hormones*, J. Lab. & Clin. Med. 25: 33, 1939.

Six young adult dogs were studied under morphine-sodium barbital anesthesia. After intravenous injection of sex hormones, heart rate, blood pressure, and respiration were recorded and followed for periods up to six hours in both intact and castrate animals. No significant alterations were noted following injection of 50 mg. of testosterone propionate, 50,000 I. U. estradiol benzoate, or 400 I. U. of theelin.

R. J. WEISSMAN

Ramos concludes that estrogen therapy should be used conservatively; that the correlation of the clinical symptomatology with the curves of folliculin constitute the most important fundamental for diagnosis and treatment in gynecic endocrine dysfunction.

CLAIR E. FOLSOME

Chiray, M., Mollard, H., and Duret, M.: *Asthma and Disturbances of the Ovarian Endocrine Secretions*, Presse méd. 48: 201, 1940.

Clinical evidence that there exists a relationship of altered ovarian activity to certain asthmatic cases can be placed in three categories: In one group the periods of the patients are normal and they note increased asthmatic attacks occurring in the premenstrual period; in a second group the asthma appears during manifest menstrual disorders and has an apparent predilection during amenorrheic episodes; last, there are those late cases of asthma which first occur with the onset of the menopause. Because of these facts one can describe those cases of asthma which are coexistent with rhythmic cycles or associated with menstrual disturbances, as ovarian asthmas.

The authors discuss 3 cases of ovarian asthma. In each the asthma was exacerbated during the inter- or premenstrual period. All 3 patients obtained excellent relief from repeated testosterone injections (10 mg.) in the premenstrual period and the writers conclude that in these cases the ovarian asthma was due to hyper-folliculinemia.

CLAIR E. FOLSOME

Heller, C. G., and Heller, Emily F.: *Gonadotropic Hormone; Urine Assays of Normally Cycling, Menopausal, Castrated, and Estrin Treated Human Females*, J. Clin. Investigation 18: 171, 1939.

Urines from 66 menopausal women were assayed by them for gonadotropic potency. It was found that their potency was not related to the presence or absence of symptoms, age, hysterectomy, or the involution. No difference in gonadotropic potency was found between menopausal women with symptoms and senile women, castrated women or menopausal women without symptoms. Urinary gonadotropic concentration was low in women with regular normal menstrual cycles, high in menopausal women in whom cycles had ceased, and intermediate in menopausal women with irregular cycles. Estrogen treatment alleviated the vasomotor symptoms of 15 menopausal women but failed to reduce concurrently their gonadotropic potency. Continued estrogen therapy caused a slight reduction in potency, but failed to suppress it by significant amounts.

J. P. GREENHILL

Bagby, B. B.: *Urinary Prolan Excretion during a Menstrual Cycle*, J. Lab. & Clin. Med. 25: 687, 1940.

The urinary prolant excretion of a normal woman was determined daily for one month, on the first morning specimen, using ovarian and uterine weights of immature rats as indicators. Prolan was found on the fifteenth and sixteenth days prior to the next menses.

HUGO EHRENFEST

Contamin, R., and Lerailliez, F.: *The Clinical Use and Therapeutic Results from Gonadotropic Hormone*, Presse méd. 47: 1660, 1939.

Sixty women with gynecologic disorders were treated with gonadotrophic hormone. Gonadotropes of both serum and urinary origin were used. The treatment was uniform in that 5 to 6 intramuscular injections, one every forty-eight hours, were given, starting the second day after the end of the period and repeated each month for three months.

Six of seven patients with secondary amenorrhea had resumption of normal menses. Five of 8 cases of juvenile primary dysmenorrhea were made better and

The injection of diethylstilbestrol, 0.25 mg. per week, for several months, produced a uterine fibrosis much less important than that inducted by the 1 mg. per week dose of estradiol benzoate. Diethylstilbestrol caused marked cystic hyperplasia of the uterine mucosa.

CLAIR E. FOLSOME

Weed, J. C., and Collins, C. G.: *The Treatment of Infant Vulvovaginitis with Estrogenic Hormone*, South. M. J. 32: 1000, 1939.

The introduction of estrogenic hormone simplified treatment of infantile vulvovaginitis and improved results. Of the three methods of administration, the oral requires at least four times the dose of the hypodermic. Vaginal suppositories have in their favor: (1) Ease of administration, an important factor in children; (2) efficient, direct action; and (3) the possibility of home treatment. Furthermore, such undesirable side effects as breast enlargement and congestion of the vulva that accompany hypodermic administration of the estrogens were not observed in this series treated by suppositories.

Estrogenic hormone causes an increase in the thickness of the stratified squamous epithelium from the six to eight cell layers of the infant vaginal mucosa to the fifteen to twenty cell layers of the adult structure, with cornification, increase of glycogen deposits, and lowered surface pH. In gonococcal vulvovaginitis histologic changes in the mucosa are accompanied by an alteration in the character of the discharge: from an excoriating, greenish one to a thick, creamy exudate containing many saprophytic gram-negative organisms with gram-positive rods, and few or no pus cells.

This report is based upon 23 cured cases of gonococcal vulvovaginitis with adequate follow-up. It is recommended as a preliminary measure to treatment that all patients be examined rectally in order to rule out the possibility of foreign body. Cleansing of the vulva with soap and warm water by the mother twice a day was employed by the gynecologic and pediatric services. The urologic service in addition used vaginal irrigations of weak potassium permanganate at each office visit. This procedure was not thought to have any particular value.

Actual treatment consisted in the nightly insertion of vaginal suppositories containing 1,000 international units of estrogenic hormone for 18 to 24 doses. Experience showed that 18,000 units was a minimal dose. The results of weekly vaginal smears served to indicate whether additional therapy was necessary. For release, four negative smears were required and follow-up examinations were made one and two months later. Of the series, there were 6 recurrences which required additional therapy. One resistant case was found to have a urethritis, and supplementary sulfanilamide therapy was given. A small hymenal opening prevented insertion of the suppository in a few cases, and it was necessary to pass a Kelly endoscope.

ARNOLD GOLDBERGER

Huet, J. A., Comte, R. J., and Hershberg, A. D.: *Diethylstilbestrol, the Synthetic Estrogenic Substance*, Gynecologia 38: 517, 1939.

The authors used stilbestrol in 46 cases and found the drug to be useful in cases of infantilism of the sex organs, in certain cases of oligomenorrhea and dysmenorrhea, in functional disturbances of the menopause and in some instances of hypophyseal-ovarian dysequilibrium. In the cases of menstrual disturbances success was observed in 77 per cent, and in the menopausal cases the incidence of relief was 82 per cent. Disagreeable symptoms such as nausea and asthenia occurred in 10 per cent of the cases, but they were serious in only 3 per cent.

The authors are enthusiastic about stilbestrol, because it is effective by mouth and it is cheap. However, as with all medication, an accurate diagnosis must be made before it is prescribed.

J. P. GREENHILL

Deanesly, Ruth: Depression of Hypophyseal Activity by the Implantation of Tablets of Oestrone and Oestradiol, *J. Endocrinol.* (London) 1: 36, 1939.

The author implanted estrone tablets, 2.25 to 16 mg.; and estradiol tablets, 11.8 to 16.5 mg., under the skin of normal male mice and rats of varying weights and permitted the tablets to remain subcutaneously for 10 to 270 days.

This treatment, like continued injections of estrogens, causes inhibition of some of the functions of the pituitary gland. It leads to marked depression of the growth rate, loss of fertility, shrinkage of gonads and accessory organs, and enlargement of the adrenals and pituitary gland. These changes, studied in detail during recovery period, were reversible after removal of the estrone or estradiol tablets.

Three rats with estradiol tablets implanted for 270 days developed tumors of the pituitary gland, which would probably eventually have proved fatal.

The author includes records showing the rate of absorption of the tablets.

CLAIR E. FOLSOME

Herrnberger, K.: The Influence of Estrin on the Vaginal Epithelium of Young Girls, *Arch. f. Gynäk.* 167: 506, 1938.

The author used estradiol benzoate in the treatment of gonorrheal vulvovaginitis in a group of 82 girls ranging in age from 6 months to 12 years. This form of hormone therapy is most efficacious, depending upon the stimulation and production of a mature vaginal mucosa. This maturation can be brought about in approximately 17 days, following a single intramuscular injection of 10,000 units of estradiol benzoate and follows such an injection in every instance. The optimum dosage, that is the least amount of hormone necessary for the maintenance of such epithelial maturation without the production of pathologic changes in the uterus and ovaries, was found to be 1,000 units of the alcoholic solution of estradiol benzoate given daily. Such daily minimal doses have no effect upon ovary or pituitary in the vast majority of instances. In the very occasional patient in whom pituitary or ovarian changes are produced no harm is done, first because such reactions are reversible and second because they tend to disappear when the medication is stopped.

RALPH A. REIS

Sharpey-Schafer, E. P., and Schrire, I.: Effect of Oestrogens on the Urinary Volume, *Lancet* 2: 973, 1939.

In a group of 14 hospitalized patients, on a controlled diet, the daily injection of 100,000 I. B. U. of estradiol benzoate for ten days did not result in a change in urinary output. The group of patients included 3 men, 3 normal menstruating, 6 postmenopausal women, and two castrate women.

CARL P. HUBER

Moricard, R., and Simard, R.: Comparative Study on the Activity of Oestradiol Benzoate, Vitamins A and C, and Diethylstilboesterol in Experimental Fibromatosis, *Ann. d'endocrinol.* 1: 399, 1939-1940.

The authors demonstrate that it is possible to produce fibromas in the female guinea pig by continuous intraperitoneal injections of estradiol benzoate, 1.0 mg. per week for four months. The fibromas can also be produced by intermittent treatment, provided the total dose of estradiol treatment remains the same.

Vitamin A (3 mg., 5000 I. U., per week intraperitoneally), when added to the estradiol benzoate did not appear to modify the production of fibrous neoplasms, uterine or abdominal, while the addition of vitamin C (100 mg., 2,000 I. U., per week intraperitoneally) to the estradiol benzoate accentuated the formation of new growths.

cases; (4) restoring the normal condition of the vulva and vagina in senile atrophic vaginitis; (5) relieving the pain of dysmenorrhea; and (6) inhibiting lactation.

Toxic effects (particularly nausea and vomiting), although not severe, developed in 21.6 per cent of patients treated with stilbestrol dipropionate and 4.5 per cent of cases treated with hexestrol. Toxic symptoms are more likely to develop when large doses are given. They also tend to disappear if treatment is persisted in.

CARL P. HUBER

Lipschutz, Alexander, and Vargas, Luis Jr.: Tumorigenic Powers of Stilboestrol and Follicular Hormones, Lancet 1: 541, 1940.

The authors corroborate their previous report that stilbestrol has a much greater tumorigenic effect than the natural estrogenic substances (estradiol and estrone). In the guinea pig, 100 to 200 mg. of estradiol per injection is necessary to produce a reaction comparable to 3 to 10 mg. of stilbestrol per injection. As much as 3 to 10 mg. of stilbestrol given three times weekly for about three months is necessary to develop uterine and extrauterine fibroids in the guinea pig. The tumorigenic action of small doses of stilbestrol is, however, less than that of similar doses of esterified estradiol (monobenzoate and dipropionate). The guinea pig uterus increases beyond the normal weight more rapidly with stilbestrol than with the free natural estrogens. This is tentatively explained by an inability of the organism to inactivate stilbestrol as rapidly and effectively. Uterine bleeding in the guinea pig is more frequent with stilbestrol than with the natural estrogens, but not more commonly encountered than with similar quantities of the esterified hormones.

CARL P. HUBER

McLellan, Archibald: Response of Non-Gravid Human Uterus to Posterior-Pituitary Extract and Its Fractions Oxytocin and Vasopressin, Lancet 1: 919, 1940.

Sixty records were obtained from 43 normal nongravid women during various stages of the menstrual cycle. All were in the reproductive age group and 34 had borne children. Uterine contractions were recorded following the insertion of a small bag. The uterus was found to respond to posterior pituitary extract immediately before and during menstruation and in the early interval phase of the cycle. Contractions of the nongravid uterus are produced by vasopressin but not at all by oxytocin.

CARL P. HUBER

Hohlweg: The Corpus Luteum Hormone Effect of Desoxycorticosteron, Zentralbl. f. Gynäk. 63: 1143, 1939.

The writer found that desoxycorticosterone produces a corpus luteum hormone effect in infantile rabbits prepared with estrin. However, this substance has only one-tenth the effect of progesterone and not one-half as claimed by Hoffmann. In castrate infantile rabbits, positive uterine reactions could not be obtained even with 80 mg. of desoxycorticosterone. The author could not produce a secretory endometrium in a single case even with much larger doses than were used by Hoffmann.

J. P. GREENHILL

Vautrin, Guillermo: Hormonal Treatment of Uterine Hyperkinesia with the Corpus Luteum Hormone, Rev. méd. cubana 51: 1, 1940.

Vautrin used the hormone of the corpus luteum as a sedative for uterine contractions in certain muscular kinesias or hypertonic conditions of the uterus in labor. He believes that successful dosage is neither in "drops nor in pitcherfuls," but in the proper amounts. It fluctuates between 10 and 20 mg. The route of introduction used was the intramuscular one. A belladonna derivative must be used in conjunction with the progesterone, if hyperkinesia is accompanied by cervical spasm.

Felding, S., and Møller-Christensen, E.: Clinical Experience with Diethylstilboestrol, *Acta obst. et gynec. Scandinav.* 19: 337, 1939.

After a short account of the biologic characteristics of Diethylstilbestrol, the writers report results obtained with the substance in 45 patients with ovarian deficiency symptoms and 10 patients with hypoplasia of the uterus. They conclude that the drug has proved to be on a par with estrone preparations. In about one-sixth of the patients, it caused nausea and vomiting, in some cases to such a degree that the treatment had to be suspended.

J. P. GREENHILL

Wenner, Robert, and Joel, Karl: Stilboestrol and Anhydro-Oxyprogesterone, *Lancet* 2: 688, 1939.

The effect of stilbestrol and anhydro-oxy-progesterone on a patient who was thirteen years postmenopausal and on 8 women castrated by x-ray therapy was studied; 25 mg. of stilbestrol by mouth or 15 mg. by intramuscular injection were required to produce proliferation of a resting or atrophic endometrium. Cystic glandular hyperplasia could be produced by 50 to 60 mg. given by mouth. The administration of 220 to 300 mg. of anhydro-oxy-progesterone produced progestational changes in the proliferated endometrium and resulted in the occurrence of a menstruation. In two of the patients fatigue, general weakness, and nausea, with vomiting in one case, appeared as side effects after stilbestrol administration. No secondary symptoms appeared after the administration of anhydro-oxy-progesterone in doses as high as 25 mg. Lactation was either prevented or inhibited in 20 women by 5 to 15 mg. of stilbestrol by mouth. In six of these cases administration of 5 to 10 mg. in a single dose during the twenty-four hours after delivery prevented the onset of lactation. In 14 cases stilbestrol was given to inhibit established lactation with satisfactory results in all but two cases. Smaller doses were effective in preventing lactation than in inhibiting established milk secretion. Doses greater than 20 mg. were not given.

CARL P. HUBER

Lorenzetti, Filiberto: Observations on the Therapeutic Properties of Diethylstilbestrol, *Gynecologia* 6: 89, 1940.

The writer has used the drug in a small series of 20 cases.

One patient was relieved of pruritus vulvae following biweekly injections of 0.5 mg. with a total dosage of 4.20 mg. Four patients having menopausal symptoms all reported relief although one patient experienced gastric disturbance with its use. Two patients with oligo- and hypomenorrhea with associated primary dysmenorrhea obtained relief from stilbestrol.

Stilbestrol used during the first six days of the puerperium in 7 cases after premature delivery of stillborn fetuses prevented lactation.

In 5 cases of surgical menopause the drug relieved vasomotor symptoms, but one patient in this group experienced nausea.

The author concludes that stilbestrol is a valuable addition to gynecologic therapy and particularly in patients presenting subestrogenic levels and in those requiring substitutional treatment during the menopause.

CLAIR E. FOLSOME

Bishop, P. M. F., et al.: Oestrogenic Properties of Stilbestrol Dipropionate and Hexoestrol, *Lancet* 1: 629, 1940.

Stilbestrol dipropionate and hexestrol have estrogenic properties similar to those of stilbestrol so far as they are capable of: (1) Inducing uterine hemorrhage in cases of amenorrhea; (2) relieving the symptoms of the menopausal syndrome; (3) leading to the appearance of cornified cells in the vaginal smear in menopausal

The author favors the prophylactic rather than the curative use of progesterone and prefers small doses frequently repeated to a few large doses. In his two cases he had difficulty in delivering the placenta. He attributes this to excessive growth of villi at the time of nidation, as the result of the progesterone.

J. P. GREENHILL

Rubinstein, H. S.: The Rationale of the Use of Testosterone Propionate in Functional Uterine Bleeding and Dysmenorrhea, *J. Lab. & Clin. Med.* 24: 1026, 1939.

Testosterone propionate in adequate dosage will relieve functional uterine bleeding and dysmenorrhea.

Ovulation is suppressed by repeated injections and the chemical similarity between this substance and progesterone may explain its progesterone-like effect. The amenorrhea following injection of large doses of testosterone propionate is probably due to the inhibition of the pituitary gland with a suppression in output of pituitary gonadotropic substance. With the diminution of estrogenic concentration, uterine relaxation is produced and this checks the continuation of the interval endometrium, and this in turn checks bleeding and pain.

W. B. SERBIN

Pierra, L. M., and Erlande, G.: The Place of the Male Hormone in Gynecology, *Rev. franç. de gynéc. et d'obst.* 35: 97, 1940.

The authors have used the male hormone in four types of female disturbances: congestive disturbances associated with ovulation, chronic mastitis, simple premenstrual congestion of the breasts, and fibroids of the uterus.

In a series of 12 women with ovulation pain only two were definitely relieved by testosterone propionate. On the other hand, 11 of 14 women with simple premenstrual mammary congestion were helped by testosterone. In cases of fibroids of the uterus, the male hormone produced cessation of excessive bleeding in the 7 cases in which it was used. However, in only 3 cases was there an apparent diminution in the size of the neoplasms.

J. P. GREENHILL

Kenny, Meave, and King, Earl: Effect of Prolactin on Lactation in Nursing Women, *Lancet* 2: 828, 1939.

Two preparations of prolactin, one from ox pituitary and the other from sheep, were administered to 43 women deficient in milk secretion, selected at times during the period of lactation varying from the immediate puerperium to eight weeks after delivery. The dosage consisted of 300 Riddle units on the first and second days of treatment, 120 units on the third and fourth days, 60 units on the fifth day of treatment. No local or systemic ill effects were noted. The response in increased milk secretion was encouraging. An increase of over three ounces of milk per day was considered a positive response. A positive response occurred in 74 per cent of the prolactin treated group, and in 21 per cent of a control group treated by nonendocrine methods. Depression of the gonadotropic function was not observed. The quality of milk secreted after the administration of the extracts was essentially the same as that of the control samples.

CARL P. HUBER

Kaijser, Kurt G.: The Effect of Prolactin on the Secretion of Milk in Women in the Puerperium and for the First Few Months After Parturition as Well as in Newborn Babies, *Acta med. Scandinav.* 104: Suppl. I-II, 1940.

Kaijser tested the lactation-stimulating and lactation-maintaining action of prolactin, administered intramuscularly, in newly delivered women, nursing mothers in whom hypogalactia later appeared and babies up to a few months old. Prolactin

As the author points out, progesterone is the antagonist of the follicle hormone and therefore, from the hormonal aspect, is the specific in cases in which the uterus reacts violently to the action of the follicular-pituitrin interrelation.

The use of the corpus luteum hormone has an advantage over morphine, because it is not toxic for the fetus. The sedative action of progesterone makes it the medicament par excellence when used in childbirth for excessively strong uterine contractions. If the inhibiting therapeutic action of progesterone produces uterine inactivity not desirable during labor, it is advisable to use pitocin (oxytocin) intravenously, especially in cases of hemorrhage.

J. P. GREENHILL

Warwick, M. H., and Parkes, A. S.: Absorption of Progesterone and Desoxycorticosterone (From Tablets Implanted Subcutaneously), *Lancet* 1: 406, 1940.

Experimental studies with the subcutaneous implantation of progesterone in the human being, goat, guinea pig, and rat reveal that from large tablets the average rate of absorption is about 20 per cent per month. Tablets weighing 50 mg. thus supply about 10 mg. per month.

Similar studies with desoxycorticosterone implanted subcutaneously in rats revealed that the rate of absorption is about twice that of desoxycorticosterone acetate. Implantation of 70 mg. tablets of the free material supplies a minimum of 4 mg. daily for one month. The use of free desoxycorticosterone is therefore suggested when heavy dosage is required.

CARL P. HUBER

Falls, Frederick H.: The Use of Progestin in Obstetrical Complications, *Illinois M. J.* 77: 180, 1940.

The author presents both clinical and laboratory evidence to prove that the use of progestin in obstetric complications, such as threatened abortion, premature separation of the placenta, and premature rupture of the membranes, is of great value, for this hormone is antagonistic toward uterine contractility and uterine irritability. In several cases where the membranes ruptured prematurely, Falls was successful in preventing the onset of uterine contractions for varying periods of time, from a few days up to a month. In 17 cases of threatened and habitual abortion, 14 patients were successfully treated with progestin. During the past year he has treated successfully 9 partial detachments of the placenta, 10 premature labors, 1 premature rupture of the membranes, 1 placenta previa, and 2 habitual abortions, whereas treatment was unsuccessful in 1 habitual abortion, 1 threatened abortion, 2 premature ruptures of the membranes, and 1 premature separation of the placenta.

EUGENE S. AUER

Beilly, Jacob S., and Solomon, Samuel: The Inhibition of Lactation Post-Partum with Testosterone Propionate, *Endocrinology* 26: 236, 1940.

In a group of 108 patients, the inhibition of lactation, post partum, by means of testosterone propionate was studied. Complete inhibition occurred in 58 per cent, incomplete results in 40 per cent. All the patients obtained relief from engorgement or distention and pain or discomfort in the breasts. Failure occurred in 2 per cent.

J. THORNWELL WITHERSPOON

Vermelin, H.: Happy Results with Progesterone in Troubles of Nidation, *Bull. Soc. d'obst. et de gynéc.* 28: 540, 1940.

The author succeeded in preventing miscarriage in two cases of threatened abortion by means of progesterone. Pains and bleeding stopped rapidly after the drug was given.

Fetal Heart Sounds.

151

1 2 1 2 1 2 1 2 1 2

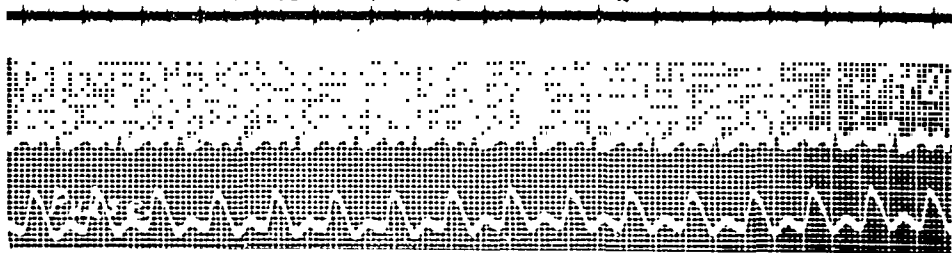


Fig. 1.—Rate 151. First sound (1) of greater intensity. Systole 0.17 to 0.18 second. Diastole 0.21 to 0.23 second. Vibrations first 5, second 4. Mother's heart rate 140.

Fetal Heart Sounds.

133

1 2 1 2 1 2 1 2 1 2

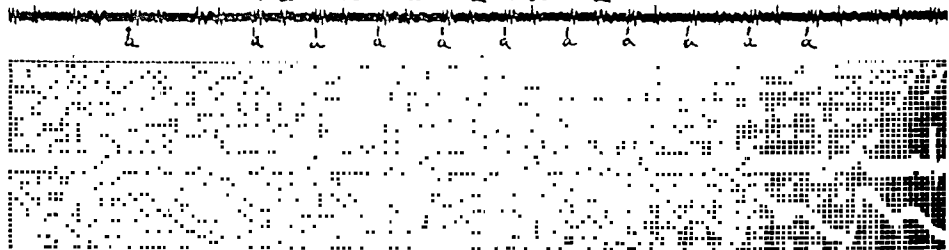


Fig. 2.—Rate 133. Heart sounds of about equal intensity. Vibrations low in frequency first (1) 1 to 3 and second (2) 3. Systole 0.16 to 0.17, diastole 0.27 to 0.29 second. Mother's rate 77. Presystolic third sound (a) is seen before every first sound but one.

Fetal Heart Sounds.

163

1 2 1 2 1 2 1 2 1 2

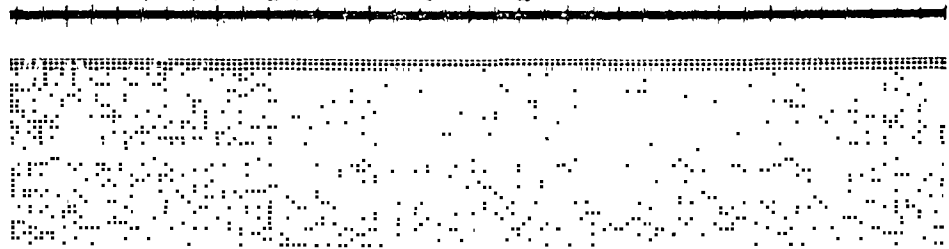


Fig. 3.—Rate 163. Second sound (2) of higher intensity and first (1) of lower frequency. Vibrations first 3 to 4 and second 1 to 3. Systole is of longer duration (0.18 to 0.19) than diastole (0.17 to 0.18 second).

Fetal Heart Sounds.

124

1 2 1 2 1 2 1 2 1 2

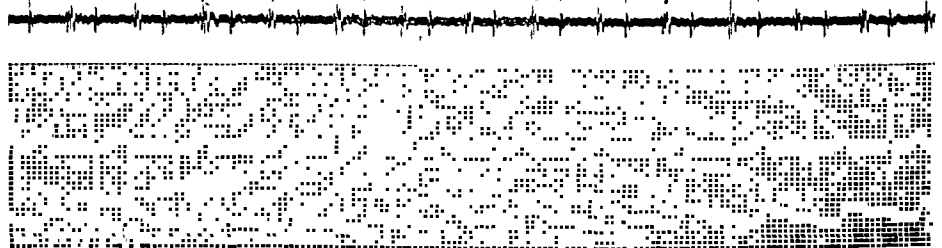


Fig. 4.—Rate 124. The second (2) is of much greater intensity and frequency. Vibrations first 3 to 5 and second 4 to 5. Systole 0.20 to 0.23 second. Diastole 0.25 to 0.27 second. Mother's rate 102.

is a hypothetical hormone of the anterior lobe of the hypophysis, which is not prepared in a chemically pure form, but is obtained in an extract from the pituitary body.

With regard to the ability of prolactin to act as a stimulus to lactation, the author's results do not definitely prove this with the dosage and the product used. However, increase in the secretion of milk was seemingly obtained in the cases in which the injections of prolactin were given relatively soon after parturition.

The author believes he has introduced a new method in the field of experimentation with prolactin, in that he studied its effect on the production of witch's milk in infants during the first few months of life. In a number of cases he succeeded in demonstrating a slight increase in the glandular tissue of the infants and in a few cases the appearance of milky fluid in very small quantities upon mild pressure on the breasts.

Finally, mention is made of the possibility of a quantitative and qualitative daily rhythm in milk secretion.

Not until the existence of such a rhythm is established and thoroughly understood will it be possible to test with any degree of certainty the action on nursing women of a hormone necessary for the institution and maintenance of lactation.

J. P. GREENHILL

Item

American Board of Obstetrics and Gynecology

In accordance with its Articles of Incorporation, the American Board of Obstetrics and Gynecology has elected Dr. Norman F. Miller of Ann Arbor, Michigan, and Dr. Willard R. Cooke of Galveston, Texas, as members, directors, and examiners, to fill the unexpired terms of Dr. Jennings C. Litzenberg and Dr. Grandison D. Royston, both of whom resigned on October 15, 1940. These replacements make a total of four changes in personnel on the Board during the past three years.

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held in June, 1941.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, from May 28 to June 1, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A (Part II) examinations must be on file in the Secretary's Office not later than March 15, 1941.

After March 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board wishes to announce a modification of the case record ruling (effective January 1, 1942) as it appears in the September, 1940, issue of the Board booklet. This ruling should read: "It is preferable that the number of residency cases submitted should not be more than half (25) of the total number of fifty (50) cases required."

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

GETTING READY TO BE A MOTHER. By Carolyn Conant Van Blarcom. Revised by Hazel Corbin, general director of Maternity Center Association. Fourth edition, 190 pages, illustrated. The Macmillan Company, New York, 1940.

CHILD CARE AND TRAINING. By Marion L. Faegre, assistant professor of parent education, and John E. Anderson, director of Institute of Child Welfare, University of Minnesota. Fifth edition, revised, 320 pages, illustrated. The University of Minnesota Press, Minneapolis, 1940.

REPORT ON THE SEX QUESTION by the Swedish Population Commission. Translated and edited by Virginia Clay Hamilton, M.D. Published for the National Committee on Maternal Health, Inc. Williams & Wilkins Company, Baltimore, 1940.

PHYSIOLOGY OF MICTURITION. By Orthello R. Langworthy, Lawrence C. Kolb and Lloyd G. Lewis, sub-department of neurology and James Buchanan Brady Urological Institute of Johns Hopkins University. 232 pages, illustrated. Williams & Wilkins Company, Baltimore, 1940.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY, with clinical and endocrine relations. By Emil Novak, associate in gynecology, Johns Hopkins Medical School, etc. 496 pages with 427 illustrations. W. B. Saunders Company, Philadelphia, 1940.

MODERN MARRIAGE. By Paul Popenoe, general director, American Institute of Family Relations, Los Angeles, Calif., etc. Second edition, 299 pages. The Macmillan Co., New York, 1940.

OBSTETRICS IN GENERAL PRACTICE. By J. P. Greenhill, M.D., professor of obstetrics and gynecology, Loyola University Medical School, Chicago, etc. 448 pages, 112 illustrations. Year Book Publishers, Inc., Chicago, 1940.

CONTROLLED FERTILITY. An evaluation of clinic service. By Regine K. Stix, M.D., research associate, Milbank Memorial Fund, and Frank W. Notestein, Ph.D., lecturer in School of Public Affairs, Princeton University. The Williams & Wilkins Company, Baltimore, 1940.

ETUDOS CIRURGICOS. By Eurico Branco Ribeiro, director do Sanatorio São Lucas. 219 pages, illustrated. Sociedade Editora Medica Limitada, São Paulo, Brasil. 1940.

LA MANIOBRA ANO PARIETO-ABDOMINAL EN LOS PROCESOS AGGUDOS DEL ABDOMEN. Por Dr. Emilio S. Sammartino. El Ateneo, liberia y editorial. Buenos Aires, 1940.

ATTAINING WOMANHOOD. By George W. Corner, M.D., professor of anatomy, University of Rochester School of Medicine. 95 pages, illustrated. Harper & Brothers, New York, 1940.

INDEX TO VOLUME 40

AUTHORS INDEX*

A

- ABARBANEL, A. R., AND GOODFRIEND, M. J., Effects of stilbestrol upon lactation, 1037
- ADAIR, FRED L., Development of maternal welfare activities, 633
- , Presidential address at American Gynecological Society sixty-fifth annual meeting, 925
- ALDRIDGE, ALBERT H., Retrodisplacement of uterus in relation to pregnancy, 361
- ALLEN, EDWARD, (WITH PARMELEE, A. H., STEIN, IRVING, F., AND BUXBAUM, HENRY), Three cases of congenital goiter, 145
- ANDERSON, GEORGE E., Treatment of pre-eclampsia, 517
- ARNELL, RUPERT E., GUERRIERO, WILLIAM F., AND IRWIN, JAMES B., Accurate roentgenologic method for determining pelvic depth, 467
- ASHTON, DOROTHY L., Analysis of 300 hysterectomies, 123
- ASHWORTH, JOHN, (WITH GALLOWAY, CHARLES EDWIN, AND SUTTON, DON C.), Acute crisis of supranrenal insufficiency complicating pregnancy, 148

B

- BARNES, ALLAN C., Method for evaluating stress of urinary incontinence, 381
- BARRIE, M. M. O., (WITH SHUTE, EVAN), Effect of estrogens on true pre-eclampsia and eclampsia, 1003
- BAUER, FRANK L., Subarachnoid injection of alcohol for treatment of pain in genital carcinoma, 278
- BEARD, B. S., (WITH TORPIN, RICHARD), Fibromyoma of uterine cervix, pedunculated and expelled from vagina, 490
- BEHNEY, CHARLES A., Carcinoma of cervix after supravaginal hysterectomy, 780
- , AND HANES, WILLIAM J., Successive coexistent tubal pregnancies, 155
- BLACK, WILLIAM C., (WITH POWELL, CUTHBERT), Extraovarian granulosa cell tumor, 318
- BLAND, P. BROOKE, Tubal pregnancy associated with tubal tuberculosis, 271
- BODANSKY, MEYER, (WITH GARDNER, HERMAN L., AND LEVINE, HARRY), Concentration of paraldehyde in blood following its administration during labor, 435
- BOMZE, EDWARD J., AND KIRSHBAUM, JACK D., Fibroma of ovary with ascites and hydrothorax, 281
- BORTNICK, A. R., (WITH HOBBS, JOHN E.), Endometriosis of lungs, 832
- BOWER, JOHN O., AND PEARCE, A. E., Prolapse and torsion of right Fallopian tube with vaginal bleeding, following vaginal hysterectomy, 1047

- BOWLES, H. E., (WITH MILNOR, G. C.), Simultaneous ovarian and intra-uterine pregnancy, 511
- BRAINARD, HOLLIS H., Renal insufficiency following transfusion of compatible blood, 142
- BROUGHER, JOHN C., Pregnancy complicated by tuboovarian abscess, 1053
- BROWN, WEBSTER H., (WITH DIPPEL, A. LOUIS), Roentgen visualization of placenta by soft tissue technique, 986
- BUXBAUM, HENRY, (WITH PARMELEE, A. H., ALLEN, EDWARD, AND STEIN, IRVING F.), Three cases of congenital goiter, 145
- BUXTON, C. L., Pregnanediol determination as aid in clinical diagnosis, 202

C

- CALDWELL, W. E., MOLOY, H. C., AND D'ESOP, D. ANTHONY, More recent conceptions of pelvic architecture, 558
- CATHCART, DON (WITH SMITH, LINTON), Viable triplets delivered by cesarean section, 515
- CHIPMAN, WALTER W., An appreciation, 547
- CINBERG, BERNARD L., New scissors for incising uterus in cesarean section, 336
- CLEMENTS, ALFRED B., (WITH SMILEY, IRVING), Chorionepithelioma of uterus, 471
- COHEN, MELVIN R., AND STEIN, IRVING F., Laboratory and clinical experience with oral pregnenolone, 713
- COHN, CLARENCE, (WITH LETONOFF, T. V., REINHOLD, JOHN G., AND RIGGS, HELENA E.), Lead mobilization accompanying toxemia of pregnancy, 1017
- CONNALLY, H. F., JR., DANN, D. I., REESE, J. M., AND DOUGLASS, L. H., Clinical study of effects of diethylstilbestrol on puerperal women, 445
- CONWAY, E. W., (WITH BOWER, JOHN O., AND PEARCE, A. E.), 1047
- CRAFTREE, E. GRANVILLE, AND REID, DUNCAN E., Pregnancy pyelonephritis in relation to renal damage and hypertension, 17
- CRON, R. S., SHUTTER, H. W., AND LAHMANN, A. H., Epidemic infectious diarrhea of newborn infant, 88

D

- DAGGS, R. G., Effect of cystine on human milk production, 457
- DAICHMAN, ISIDORE, (WITH POMERANCE, WILLIAM), Effect of salt poor diet during pregnancy upon duration of labor, 463
- DAMON, VIRGIL G., (WITH SCUDDER, JOHN, AND DREW, CHARLES R.), Studies on preservation of placental blood, 461
- D'AMOUR, FRED E., Further studies on hormone excretion during menstrual cycle, 958

*July, pp. 1-180; August, pp. 181-360; September, pp. 361-544; October, pp. 545-726; November, pp. 727-924; December, pp. 925-1106.

- DANFORTH, W. C., Unmarried mother as medical and social problem, 637
- DANN, D. I., (WITH CONNALLY, H. F., JR., REESE, J. M., AND DOUGLASS, L. H.), Clinical study of effects of diethylstilbestrol on puerperal women, 445
- DANNREUTHER, WALTER T., Designation of specialists by American Board of Obstetrics and Gynecology, 671
- DER BRUCKE, M. G., Intestinal obstruction due to malignancy complicating pregnancy, 307
- D'ESOP, D. ANTHONY, (WITH CALDWELL, W. E., AND MOLOY, H. C.), More recent conceptions of pelvic architecture, 558
- DICKINSON, ROBERT LATOU, Application of sculpture to practical teaching in obstetrics, 662
- DIDDLE, A. W., (WITH KEETTEL, W. C., AND PLASS, E. D.), Premature elective rupture of membranes, 225
- DIECKMANN, WILLIAM J., AND KRAMER, S., Treatment of oliguria and anuria, 61
- DILL, L. V., STANDER, H. J., AND ISENHOUR, C. E., Evaluation of effect of antenatal antisyphilitic therapy on fetal mortality and on congenital syphilis, 965
- DIPPEL, A. LOUIS, AND BROWN, WEBSTER H., Roentgen visualization of placenta by soft tissue technique, 986
- DOCKERTY, MALCOLM B., AND MASSON, JAMES C., Unusual coexistence of squamous cell carcinoma and cervical fibromyoma, 477
- DOUGLASS, L. H., (WITH CONNALLY, H. F., JR., DANN, D. I., AND REESE, J. M.), Clinical study of effects of diethylstilbestrol on puerperal women, 445
- DREW, CHARLES R., (WITH SCUDDER, JOHN, AND DAMON, VIRGIL G.), Studies on preservation of placental blood, 461

E

- EASTMAN, NICHOLSON J., Apnea neonatorum, 647
- , (WITH HELLMAN, L. M., AND SHETTLES, L. B.), Vitamin K in obstetrics, 844
- EHRENFEST, HUGO, Pregnancy and disease, 596
- ELLISON, EUGENE T., Obstructed labor due to fetal ascites, 1057
- ENGE, LUDWIG A., Functional and growth characteristics of struma ovarii, 738
- ERVING, HENRY W., SEARS, CHRISTINE, AND ROCK, JOHN, Clinical experiences with equine gonadotropic hormone, 695

F

- FALLS, FREDERICK H., Simple method of making an artificial vagina, 906
- FENNING, CON, Mechanical ink writing recorder suitable for recording uterine motility during pregnancy and labor, 330
- FINCH, J. WILLIAM, Nausea and vomiting of pregnancy due to allergic reaction, 1029
- FISHER, JOHN H., Chorioangioma of placenta, 493
- FITZGERALD, J. E., AND WEBSTER, AUGUSTA, Effect of vitamin K administered to patients in labor, 413
- FLEMING, EDWARD A., AND KAVA, HARRY L., Congenital atresia of upper two-thirds of vagina and cervical os with hematometra, 296

- FLUHMAN, C. F., Twenty years of progress in endocrine studies of reproduction, 609
- FRALIN, FLORENCE G., (WITH WILLIAMS, PHILIP F., AND HARK, BERNARD), Nutrition study in pregnancy, 1
- , (WITH WILLIAMS, PHILIP F., AND GRIFFITH, GEORGE C.), Relation of vitamin B₁ to reproductive cycle, 181
- FRANK, ROBERT T., Certain outstanding trends in gynecology during past forty years, 574
- FRANKEL, LEONARD, (RAGINS, ALEX B.), Intraligamentous granulosa cell tumor, 302
- FRASER, C. K., AND JONES, J. W., Paraldehyde analgesia and perineal anesthesia in obstetrics, 506

G

- GALLOWAY, CHARLES EDWIN, SUTTON, DON C., AND ASHWORTH, JOHN, Acute crisis of suprarenal insufficiency complicating pregnancy, 148
- GARDNER, GEORGE H., Fibromyoma angiomatous of uterus, 822
- GARDNER, HERMAN L., LEVINE, HARRY, AND BODANSKY, MEYER, Concentration of paraldehyde in blood following its administration during labor, 435
- GEILING, E. M. K., Comparative anatomy and pharmacology of pituitary gland of unusual "experimental" animals, 727
- GEIST, S. H., (WITH SALMON, U. J., AND WALTER, R. I.), Evaluation of stilbestrol as therapeutic estrogen, 243
- GOLDBLATT, MYRON, E., AND SCHWARTZ, HAROLD A., Correlation of Friedman test and phase of endometrium in ectopic pregnancy, 233
- GOODALL, JAMES R., AND QUINN, LOUIS J., Prevention of postoperative traumatic and catheter cystitis, 338
- GOODFRIEND, M. J., (WITH ABARBANEL, A. R.), Effects of stilbestrol upon lactation, 1037
- GORDON, CHARLES A., AND ROSENTHAL, ALEXANDER H., Use of sulfanilamide in obstetrics and gynecology, 211
- GRAFFAGNINO, PETER, (WITH HALPERT, BÉLA), Acute inversion of uterus postpartum associated with placenta accreta, 509
- GRIFFITH, GEORGE C., (WITH WILLIAMS, PHILIP F., AND FRALIN, FLORENCE G.), Relation of vitamin B₁ to reproductive cycle, 181
- GUERRIERO, WILLIAM F., (WITH ARNELL, RUPERT E., AND IRWIN, JAMES B.), Accurate roentgenologic method for determining pelvic depth, 467

H

- HALPERT, BÉLA, AND GRAFFAGNINO, PETER, Acute inversion of uterus postpartum associated with placenta accreta, 509
- HAMBLIN, E. C., Endocrine therapy of functional ovarian failure, 615
- HANES, WILLIAM J., (WITH BEHNEY, CHARLES A.), Successive, coexistent tubal pregnancies, 155
- HARK, BERNARD, (WITH WILLIAMS, PHILIP F., AND FRALIN, FLORENCE G.), Nutrition study in pregnancy, 1
- HAUMEDER, EVA, Bilateral fibroma of ovaries combined with degenerating adenoma of right breast, 514
- HEALY, WILLIAM P., Evaluation of treatment of uterine cancer, 578

- HEAVER, W. LYNWOOD, Psychiatric contraindications in use of estrogens during menopause, 980
- HELLMAN, L. M., SHETTLES, L. B., AND EASTMAN, N. J., Vitamin K in obstetrics, 844
- HERVERT, W. J., (WITH SMITH, ARTHUR L.), Method for recording and reproducing fetal heart sounds, 102
- HESELTYNE, H. CLOSE, Vulval and vaginal mycosis and trichomoniasis, 641
- HIRST, JOHN C., AND SHOEMAKER, ROBERT E., Vitamin A in pregnancy, 12
- HOBBS, JOHN E., AND BORTNICK, A. R., Endometriosis of lungs, 832
- HOFFMAN, BYRON J., Carcinosarcoma of uterus, 289
- HUFFMAN, JOHN W., Evaluation of androgenic therapy in gynecologic practice, 675
- HUGHES, EDWARD C., Relationship of thyroid and adrenal glands to toxemias of pregnancy, 48

I

- IRVING, FREDERICK C., Modern trends in artificial termination of pregnancy and labor, 621
- IRWIN, JAMES B., (WITH ARNELL, RUPERT E., AND GUERRIERO, WILLIAM F.), Accurate roentgenologic method for determining pelvic depth, 467
- ISENHOUR, C. E., (WITH DILL, L. V., AND STANDER, H. J.), Evaluation of effect of antenatal antisiphilitic therapy on fetal mortality and on congenital syphilis, 965

J

- JACOBS, J. BAY, Film scales for use in pelvimetric roentgenography, 150
- JACOX, HAROLD W., (WITH STANTON, JAMES N., JR.), Benign postirradiation stricture and primary carcinoma of colon, 486
- JAFFE, BORIS, (WITH WEINTRAUB, FREDERICK), Acute intestinal obstruction complicating pregnancy and postpartum period, 481
- JAVERT, CARL T., Intrauterine onset of hemorrhagic disease of newborn, 453
- , AND MOORE, ROBERT A., Prothrombin concentration in parturient women and their newborn infants, 1022
- JONES, J. W., (WITH FRASER, C. K.), Paraldehyde analgesia and perineal anesthesia in obstetrics, 506

K

- KANE, HOWARD F., Use of helium and oxygen in treatment of asphyxia neonatorum, 140
- KAUFMAN, MORTON S., (WITH KOTZ, J.), Technique for rectal administration of paraldehyde, 332
- KAVA, HARRY L., (WITH FLEMMING, EDWARD A.), Congenital atresia of upper two-thirds of vagina and cervical os with hematometra, 296
- KEETTEL, W. C., DIDDLE, A. W., AND PLASS, E. D., Premature elective rupture of membranes, 225
- KELSO, JOSEPH W., Cobra venom for intractable pain, 1050
- KIMBROUGH, ROBERT A., JR., AND TOMPKINS, PENDLETON, Removal of Gräfenburg ring without interruption of pregnancy, 156
- KING, EDWARD L., Comparison of two cesarean section surveys carried on in City of New Orleans, 860

- KIRSHBAUM, JACK D., (WITH BOMZE, EDWARD J.), Fibroma of ovary with ascites and hydrothorax, 281
- KLEIN, MILTON D., (WITH TAMIS, ABRAHAM B.), Critical analysis of cesarean section in large municipal hospital, 250
- KOSMAK, GEORGE W., Contraceptive practices, 652
- KOTZ, J., AND KAUFMAN, MORTON S., Technique for rectal administration of paraldehyde, 332
- KRAMER, S., (WITH DIECKMANN, WILLIAM J.), Treatment of oliguria and anuria, 61

L

- LACKNER, JULIUS E., SCHILLER, WALTER, AND TULSKY, ALEX S., Coincidence of tuberculosis of endometrium with tuberculosis of lung, 429
- LAHMANN, A. H., (WITH CRON, R. S., AND SHUTTER, H. W.), Epidemic infectious diarrhea of newborn infant, 88
- , AND SCHWARTZ, S. F., Pelvic tuberculosis, 439
- LANSMAN, HENRY H., (WITH MENCKEN, HARRY P.), Results in treatment of 600 incomplete abortions, 1011
- LE VINE, I., AND WOLF, I. J., Difficult labor due to amorphous monster, 327
- LEE, GEORGE BOLLING, AND STONE, EUGENE T. RUSH, Bilateral simultaneous tubal pregnancy, 316
- LETONOFF, T. V., REINHOLD, JOHN G., RIGGS, HELENA E., AND COHN, CLARENCE, Lead mobilization accompanying toxemia of pregnancy, 1017
- LEVINE, HARRY, (WITH GARDNER, HERMAN L., AND BODANSKY, MEYER), Concentration of paraldehyde in blood following its administration during labor, 435
- LONGWELL, FREEMAN H., (WITH MENGERT, WILLIAM F.), Prolapse of umbilical cord, 79
- LOUNSBURY, JAMES B., Reduction of postpartum morbidity by prophylactic use of ergonovine, 111
- LUICKART, RALPH, New forceps possessing sliding lock, modified fenestra, with improved handle and axis traction attachment, 1058
- LULL, CLIFFORD B., Abdominal pregnancy, 194
- LUND, CURTIS J., Recognition and treatment of fetal heart arrhythmias due to anoxia, 946

M

- MACKLIN, MADGE THURLOW, Correspondence, 540
- MAEDER, EDWARD C., AND MYERS, J. ARTHUR, Significance of tuberculin test in pregnancy, 218
- MARCHETTI, ANDREW A., Endometrium-like mucosa lining Fallopian tube, 69
- MARTZLOFF, KARL H., Primary cancer of Fallopian tube, 804
- MARX, JOHANN R., Pregnancy and fever therapy, 1056
- MASSON, JAMES C., (WITH DOCKERTY, MALCOLM B.), Unusual coexistence of squamous cell carcinoma and cervical fibromyoma, 477
- MAYER, VICTOR, (WITH ZUPP, LOUIS J.), Traumatic hematoma of omental adhesions simulating premature separation of placenta, 513

- McDONALD, JOHN R., (WITH SKINNER, IRA C.), Mixed adenocarcinoma and squamous cell carcinoma of uterus, 258
- McGOOGAN, LEON S., Isolated paralysis of serratus anterior muscle during puerperium, 313
- MEIGS, JOE VINCENT, (WITH NATHANSON, IRA T., AND RICE, CHARLOTTE), Hormonal studies in artificial menopause produced by roentgen rays, 936
- MENCKEN, HARRY P., AND LANSMAN, HENRY H., Results in treatment of 600 incomplete abortions, 1011
- MENGERT, WILLIAM F., AND LONGWELL, FREEMAN H., Prolapse of umbilical cord, 79
- MILLER, NORMAN F., Carcinoma of body of uterus, 791
- MILNOR, G. C., AND BOWLES, H. E., Simultaneous ovarian and intrauterine pregnancy, 511
- MOLOY, H. C., (WITH CALDWELL, W. E., AND D'ESOP, D. ANTHONY), More recent conceptions of pelvic architecture, 558
- MOORE, ROBERT A., (WITH JAVERT, CARL T.), Prothrombin concentration in parturient women and their newborn infants, 1022
- MOORE, THOMAS V., Moral aspects of therapeutic abortion, 422
- MUCKLÉ, CRAIG W., Suppression of lactation by stilbestrol, 133
- , (WITH PAYNE, FRANKLIN L.), Stilbestrol in treatment of menopausal symptoms, 135
- MYERS, J. ARTHUR, (WITH MAEDER, EDWARD C.), Significance of tuberculin test in pregnancy, 218

N

- NATHANSON, IRA T., RICE, CHARLOTTE, AND MEIGS, JOE VINCENT, Hormonal studies in artificial menopause produced by roentgen rays, 936
- NEIGUS, IRWIN, (WITH WOLFE, SAMUEL A.), Erythroblastosis fetalis, 31
- NEWBERY, HELEN, (WITH SONTAG, LESTER WARREN), Normal variations of fetal heart rate during pregnancy, 449
- NICHOLS, RICHARD B., Relation of obstetric complications to sterility, 276
- NOVAK, EMIL, Management of menopause, 589

O

- OBERST, FRED W., AND PLASS, E. D., Calcium, Phosphorus, and nitrogen metabolism in women during second half of pregnancy and in early lactation, 399

P

- PARMELEE, A. H., ALLEN, EDWARD, STEIN, IRVING F., AND BUXBAUM, HENRY, Three cases of congenital goiter, 145
- PAXSON, NEWLIN F., Chronic nephritis and pregnancy fatalities in Philadelphia, 995
- PAYNE, FRANKLIN L., AND MUCKLÉ, CRAIG WRIGHT, Stilbestrol in treatment of menopausal symptoms, 135
- PEARCE, A. E., (WITH BOWER, JOHN O.), Prolapse and torsion of right Fallopian tube with vaginal bleeding, following vaginal hysterectomy, 1047
- PEMBERTON, FRANK A., Carcinoma of ovary, 751

- PHANEUF, LOUIS E., Progress of cesarean section, 603
- PIPER, MONTE C., Primary diffuse adenocarcinoma of vagina, 498
- PLASS, E. D., Increase in hospital deliveries, 659
- , (WITH KEETTEL, W. C., AND DIDDLE, A. W.), Premature elective rupture of membranes, 225
- , (WITH OBERST, FRED W.), Calcium, phosphorus, and nitrogen metabolism in women during second half of pregnancy and in early lactation, 399
- , (WITH TRUSSELL, RAY E.), Pathogenicity and physiology of pure culture of trichomonas vaginalis, 883
- POMERANCE, WILLIAM, AND DAICHMAN, ISIDORE, Effect of salt poor diet during pregnancy upon duration of labor, 463
- POWELL, CUTHBERT, AND BLACK, WILLIAM C., Extraovarian granulosa cell tumor, 318
- PRATT, J. P., Pseudohermaphroditism, 870

Q

- QUINN, LOUIS J., (WITH GOODALL, JAMES R.), Prevention of postoperative traumatic and catheter cystitis, 338

R

- RAGINS, ALEX B., AND FRANKEL, LEONARD, Intraligamentous granulosa cell tumor, 302
- RECORDS, J. W., Velamentous insertion of umbilical cord, 504
- REESE, J. M., (WITH CONNALLY, H. F., JR., DANN, D. I., AND DOUGLASS, L. H.), Clinical study of effects of diethylstilbestrol on puerperal women, 445
- REID, DUNCAN E., (WITH CRABTREE, GRANVILLE E.), Pregnancy pyelonephritis in relation to renal damage and hypertension, 17
- REINHOLD, JOHN G., (WITH LETONOFF, T. V., RIGGS, HELENA E., AND COHN, CLARENCE), Lead mobilization accompanying toxemia of pregnancy, 1017
- RICE, CHARLOTTE, (WITH NATHANSON, IRA T., AND MEIGS, JOE VINCENT), Hormonal studies in artificial menopause produced by roentgen rays, 936
- RIGGS, HELENA E., (WITH LETONOFF, T. V., REINHOLD, JOHN G., AND COHN, CLARENCE), Lead mobilization accompanying toxemia of pregnancy, 1017
- RITTER, FRED L., AND STRINGER, SYDNEY W., Lipoma of uterus, 501
- ROCK, JOHN, (WITH ERVING, HENRY W., AND SEARS, CHRISTINE), Clinical experiences with equine gonadotropic hormone, 695
- ROSENTHAL, ALEXANDER H., (WITH GORDON, CHARLES A.), Use of sulfanilamide in obstetrics and gynecology, 211
- ROZIN, SAMUEL, (WITH ZONDEK, BERNHARD, AND VESELL, MORTON), Uterine bleeding induced by progesterone, 391
- RUBIN, I. C., Uterotubal insufflation as test for tubal patency, 1920-1940, 628
- RUNNELS, SCOTT C., Small hospital as obstetric hazard, 347
- , AND WYLIE, BURDETT, Stillbirths and neonatal deaths, 526

S

- SALMON, U. J., GEIST, S. H., AND WALTER, R. I., Evaluation of stilbestrol as therapeutic estrogen, 243
- SAMPSON, JOHN A., Development of implantation theory for origin of peritoneal endometriosis, 549
- SCHATTENBERG, HERBERT J., AND ZISKIND, JOSEPH, Right uterus unicornis associated with renal agenesis, 293
- SCHILLER, WALTER, (WITH LACKNER, JULIUS E., AND TULSKY, ALEX S.), Coincidence of tuberculosis of endometrium with tuberculosis of lung, 429
- SCHWARTZ, HAROLD A., (WITH GOLDBLATT, MYRON E.), Correlation of Friedman test and phase of endometrium in ectopic pregnancy, 233
- SCHWARTZ, S. F., (WITH LAHMANN, A. H.), Pelvic tuberculosis, 439
- SCUDDER, JOHN, DREW, CHARLES R., AND DAMON, VIRGIL G., Studies on preservation of placental blood, 461
- SEARS, CHRISTINE, (WITH ERVING, HENRY W., AND ROCK, JOHN), Clinical experiences with equine gonadotropic hormone, 695
- SHANNON, WILLIAM F., Spontaneous rupture of spleen complicating labor, 323
- SHARKEY, WILLIAM P., Pubiotomy in impacted mentum posterior presentation, 267
- SHETTLES, L. B., (WITH HELLMAN, L. M., AND EASTMAN, N. J.), Vitamin K in obstetrics, 844
- SHOEMAKER, ROBERT E., (WITH HIRST, JOHN C.), Vitamin A in pregnancy, 12
- SHUTE, EVAN, AND BARRIE, M. M. O., Effect of estrogens on true pre-eclampsia and eclampsia, 1003
- SHUTTER, H. W., (WITH CRON, R. S., AND LAHMANN, A. H.), Epidemic infectious diarrhea of newborn infant, 88
- SIEGEL, ISADORE A., Brenner Tumor of ovary complicating labor, 337
- SKINNER, IRA C., AND McDONALD, JOHN R., Mixed adenocarcinoma and squamous cell carcinoma of uterus, 258
- SMILEY, IRVING, AND CLEMENTS, ALFRED B., Chorionepithelioma of uterus, 471
- SMITH, ARTHUR L., AND HERVERT, W. J., Method for recording and reproducing fetal heart sounds, 102
- SMITH, LINTON, AND CATHCART, DON, Viable triplets delivered by cesarean section, 515
- SMITH, PHILIP H., Study of 1,200 cases of hysterectomy, 118
- SONTAG, LESTER WARREN, AND NEWBERY, HELEN, Normal variations of fetal heart rate during pregnancy, 449
- STANDER, H. J., (WITH DILL, L. V., AND ISNHOOR, C. E.), Evaluation of effect of antenatal antisiphilitic therapy on fetal mortality and on congenital syphilis, 965
- STANTON, JAMES N., JR., AND JACOX, HAROLD W., Benign postirradiation stricture and primary carcinoma of colon, 486

- STEIN, IRVING F., (WITH COHEN, MELVIN R.), Laboratory and clinical experience with oral pregnenolone, 713
- , (WITH PARMELEE, A. H., ALLEN, EDWARD, AND BUXBAUM, HENRY), Three cases of congenital goiter, 145
- STONE, EUGENE T. RUSH, (WITH LEE, GEORGE BOLLING), Bilateral simultaneous tubal pregnancy, 316
- STREETER, GEORGE L., Changes in trend of embryologic research, 626
- STRINGER, SYDNEY, (WITH RITTER, FRED L.), Lipoma of uterus, 501
- SUTTON, DON C., (WITH GALLOWAY, CHARLES EDWIN, AND ASHWORTH, JOHN), Acute crisis of suprarenal insufficiency complicating pregnancy, 148

T

- TAMIS, ABRAHAM B., AND KLEIN, MILTON D., Critical analysis of cesarean section in large municipal hospital, 250
- TAUSSIG, FRED J., Cancer of vulva, 764
- TAYLOR, HOWARD C., JR., Changing conceptions of ovarian tumors, 566
- TAYLOR, K. P. A., Operation for uterine retrodisplacement and prolapse by reduction and attachment of round ligaments, 1026
- THOMS, HERBERT, "Anesthésie à la Reine," 340
- , Roentgen pelvimetry as routine prenatal procedure, 891
- TOMPKINS, PENDLETON, (WITH KIMBROUGH, ROBERT A., JR.), Removal of Gräfenburg ring without interruption of pregnancy, 156
- TORPIN, RICHARD, AND BEARD, B. C., Fibromyoma of uterine cervix, pedunculated and expelled from vagina, 490
- TRUSSELL, RAY E., AND PLASS, E. D., Pathogenicity and physiology of pure culture of trichomonas vaginalis, 883
- TULSKY, ALEX S., (WITH LACKNER, JULIUS E., AND SCHILLER, WALTER), Coincidence of tuberculosis of endometrium with tuberculosis of lung, 429
- TURELL, ROBERT, Tattooing (puncturation) with mercury sulfide for treatment of intractable pruritus caused by leucoplakia-kraurosis vulvae, 334

V

- VESELL, MORTON, (WITH ZONDEK, BERNHARD, AND ROZIN, SAMUEL), Uterine bleeding induced by progesterone, 391
- VISHER, J. W., Weighted abdominal retractor, 516
- VOGT, CLIFFORD J., Granulosa cell tumor of ovary with hemoperitoneum and hemothorax, 285

W

- WALLACE, J. THORNTON, Uterine bleeding in last trimester of pregnancy, 128
- WALTER, R. I., (WITH SALMON, U. J., AND GEIST, S. H.), Evaluation of stilbestrol as therapeutic estrogen, 243

- WARD, GEORGE GRAY, Evaluation of hospital statistics, 655
—, Radium therapy in gynecology, 158
WATSON, B. P., Puerperal infection, 584
WEBSTER, AUGUSTA, (WITH FITZGERALD, J. E.), Effect of vitamin K administered to patients in labor, 413
WEINTRAUB, FREDERICK, AND JAFFE, BORIS, Acute intestinal obstruction complicating pregnancy and postpartum period, 481
WILLIAMS, PHILIP F., GRIFFITH, GEORGE C., AND FRALIN, FLORENCE G., Relation of vitamin B₁ to reproductive cycle, 181
—, HARK, BERNARD, AND FRALIN, FLORENCE G., Nutrition study in pregnancy, 1
WILSON, KARL M., Management of adherent placenta in presence of infection, 854
WINKELSTEIN, L. B., Effect of thyroid on sterility in normal and hypothyroid females, 94
WOLF, I. J., (WITH LE VINE, I.), Difficult labor due to amorphous monster, 327
WOLFE, SAMUEL A., AND NEIGUS, IRWIN, Erythroblastosis fetalis, 31
WYLIE, BURDETT, (WITH RUNNELS, SCOTT C.), Stillbirths and neonatal deaths, 526
- Z
- ZISKIND, JOSEPH, (WITH SCHATTENBERG, HERBERT J.), Right uterus unicornis associated with renal agenesis, 293
ZONDEK, BERNHARD, ROZIN, SAMUEL, AND VESELL, MORTON, Uterine bleeding induced by progesterone, 391
ZUPP, LOUIS J., AND MAYER, VICTOR, Traumatic hematoma of omental adhesions simulating premature separation of placenta, 513

SUBJECT INDEX*

A

- Abdominal pregnancy (Lull), 194
 retractor, weighted (Visser), 516
 surgery, gynecologic, method of getting patients out of bed early after (Charbonnier), 540 (Abst.)
- Abortions, febrile, sulfanilamide therapy in (Mencken and Lansman), 1013
 incomplete, results in treatment of 600 (Mencken and Lansman), 1011
 therapeutic, moral aspects of (Moore), 422
- Abscess, tuboovarian, pregnancy complicated by (Brougher), 1053
- Abstracts and reviews, department of, 172, 533, 534, 918, 1076
 endocrinology, 1076
 gynecologic operations, 534
 miscellaneous, 16, 47, 110, 139, 147, 149, 157, 193, 301, 329, 380, 428, 466, 492, 512, 945, 1021, 1036, 1060
 myoma and endometrioma, 172
 physiology of pregnancy, 353
 sterility, 918
- Adenocarcinoma, mixed, and squamous cell carcinoma of uterus (Skinner and McDonald), 258
 primary diffuse, of vagina (Piper), 498
- Adenoma of right breast, bilateral fibroma of ovaries combined with degenerating (Haumeder), 514
- Adhesions, omental, traumatic hematoma of, simulating premature separation of placenta (Zupp and Mayer), 513
- Adnexal inflammation, permeability of tubes in, research on (Daniel, Mavrodin, and Wanef), 918 (Abst.)
- Adrenal glands, relationship of, and thyroid, to toxemias of pregnancy (Hughes), 48
- Agensis, renal, right uterus unicornis associated with (Schattenberg and Ziskind), 293
- Alcohol, subarachnoid injection of, for treatment of pain in genital carcinoma (Bauer), 278
- Allergic reaction, nausea and vomiting of pregnancy due to (Finch), 1029
- Apnea neonatorum (Eastman), 647
- Amenorrhea (Erving, Sears, and Rock), 710
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons, officers of, 179, 725
 Board of Obstetrics and Gynecology, Inc., Candidates certified in June, 1940, 176
 designation of specialists by (Dannreuther), 671
 items of, 176, 360, 544, 924, 1087
 Gynecological Society, officers of, 179, 725
 papers of, 727-917, 925-935
 presidential address (Adair), 925
 Medical Association Section of Obstetrics and Gynecology, officers of, 179, 725
 obstetrical and gynecological societies, roster of, 179, 725
- Analgesia, paraldehyde, and perineal anesthesia in obstetrics (Fraser and Jones), 506

- Androgenic hormones (Fluhmann), 613
 therapy in gynecologic practice, evaluation of (Huffman), 675
- Androgens (Hamblen), 618
- Androsterone (Fluhmann), 613
- Anemia hemolytica neonatorum (Wolfe and Neigus), 44
- Anesthesia, art of (Flagg), 1071 (B. Rev.)
 cyclopropane (Robbins), 1074 (B. Rev.)
 history of, chapter in (Thoms), 340
 perineal, and paraldehyde analgesia in obstetrics (Fraser and Jones), 506
 spinal, headaches after, explanation for (Vrba), 512 (Abst.)
- Anesthésie à la Reine (Thoms), 340
- Anhydro-oxypregesterone and stilbestrol (Wenner and Joel), 1083 (Abst.)
- Announcement, 360, 361
- Anoxia, fetal heart arrhythmias due to, recognition and treatment of (Lund), 946
- Antenatal antisyphilitic therapy, evaluation of effect of, on fetal mortality and on congenital syphilis (Dill, Stander, and Isenhour), 965
- Anteron (Erving, Sears, and Rock), 695
- Anuria and oliguria, treatment of (Dieckmann and Kramer), 61
- Architecture, pelvic, more recent conceptions of (Caldwell, Moloy, and D'Esopo), 558
- Arrhythmias, fetal heart, due to anoxia, recognition and treatment of (Lund), 946
- Artificial vagina, simple method of making (Falls), 906
- Ascites and hydrothorax, fibroma of ovary with (Bomze and Kirshbaum), 281
 fetal, obstructed labor due to (Ellison), 1057
- Asphyxia neonatorum, treatment of, use of helium and oxygen in (Kane), 140
- Asthma and disturbances of ovarian endocrine secretions (Chiray, Molard, and Duret), 1079 (Abst.)
- Atresia, congenital, of tricuspid valve complicated by congenital myxosarcoma of labium majus (Amolsch), 149 (Abst.)
 congenital, of upper two-thirds of vagina and cervical os with hematometra (Flemming and Kava), 296

B

- Baldy-Webster operation by vaginal route (Barros), 537 (Abst.)
- Baltimore Obstetrical and Gynecological Society, officers of, 179, 725
- Bilateral simultaneous tubal pregnancy (Lee and Stone), 316
- Biochemistry of disease (Bodansky and Bodansky), 1070 (B. Rev.)
- Biological Symposia (Cattell), 1070 (B. Rev.)
- Bleeding, frequency and etiology of (Ward), 159
 uterine, functional, clinical correlates of (Hamblen), 1076 (Abst.)

*July, pp. 1-180; August, pp. 181-360; September, pp. 361-544; October, pp. 545-726; November, pp. 727-924; December, pp. 925-1106.

- Bleeding, uterine—Cont'd
 in last trimester of pregnancy (Wallace), 128
 induced by progesterone (Zondek, Rozin, and Vesell), 391
- Blood, compatible, transfusion of, renal insufficiency following (Brainard), 142
 in pregnancy, composition of (Ramsay, Thierens, and Magee), 355 (Abst.)
 paraldehyde in, concentration of, following its administration during labor (Gardner, Levine, and Bodansky), 435
 placental, preservation of, studies on (Scudder, Drew, and Damon), 461
 studies as guide to therapy (Scudder), 1073 (B. Rev.)
 venous, hematology of sternal marrow and, of pregnant and nonpregnant women (Pitts and Packham), 355 (Abst.)
 vitamin C in, concentration of, during and after pregnancy (Sadovsky, Weber, and Wertheimer), 357 (Abst.)
- Book reviews, department of, 1061
- Books received, 180, 359, 525, 924, 1088
- Breast, adenoma of, right, bilateral fibroma of ovaries combined with degenerating (Haumeder), 514
- Brenner tumor of ovary complicating labor (Siegel), 337
- Brooklyn Gynecological Society, officers of, 179, 725
 transactions of, 171
- C
- Calcium metabolism, phosphorus, and nitrogen, in women during second half of pregnancy and in early lactation (Oberst and Plass), 399
- Cancer of cervix, radium therapy in (Ward), 164
 of vulva (Taussig), 764
 primary, of Fallopian tube (Martzloff), 804
 uterine, treatment of, evaluation of (Healy), 578
 youth looks at, 1075 (B. Rev.)
- Carcinoma, genital, pain in, treatment of, subarachnoid injection of alcohol for (Bauer), 278
 of body of uterus (Miller), 791
 of cervix after supravaginal hysterectomy (Behney), 780
 uteri, intractable pain in, relief of (Todd), 492 (Abst.)
 of ovary (Pemberton), 751
 primary, of colon, benign postirradiation stricture and (Stanton, Jr., and Jacox), 486
 squamous cell, coexistence of, unusual, and cervical fibromyoma (Dockerty and Masson), 477
 of uterus, mixed adenocarcinoma and (Skinner and McDonald), 258
- Carcinosarcoma of uterus (Hoffman), 289
- Central Association of Obstetricians and Gynecologists, item of, 544
 officers of, 179, 725
- Cervical fibromyoma, coexistence of, unusual, and squamous cell carcinoma (Dockerty and Masson), 477
 os, congenital atresia of upper two-thirds of vagina and, with hematometra (Flemming and Kava), 296
- Cervix, cancer of, radium therapy in (Ward), 164
 carcinoma of, after supravaginal hysterectomy (Behney), 780
 tuberculosis of (Lahmann and Schwartz), 439
 uterine, fibromyoma of, pedunculated and expelled from vagina (Torpin and Beard), 490
- Cesarean section (Irving), 622
 in large municipal hospital, critical analysis of (Tamis and Klein), 250
 lower segment operation (Marshall), 1066 (B. Rev.)
 progress of (Phaneuf), 603
 scissors for incising uterus in (Cinberg), 336
 surveys carried on in New Orleans, comparison of two (King), 860
 triplets, viable, delivered by (Smith and Cathcart), 515
- Chicago Gynecological Society, officers of, 179, 725
 transactions of, 170, 171, 533, 724
- Chorioangioma of placenta (Fisher), 493
- Chorionepithelioma of uterus (Smiley and Clements), 471
- Chorionic gonadotropins (Hamblen), 616
- Cigarette smoke, effects of nicotine and, on pregnant albino rats and their offspring (Essenberg, Schwind, and Patras), 380 (Abst.)
- Cincinnati Obstetrical Society, officers of, 179, 725
- Circulatory disturbances and folliculin psychoses (Baruk, David, Racine, and Mlle. Leuret), 1078 (Abst.)
- Cobra venom for intractable pain (Kelso), 1050
- Colon, carcinoma of, primary, benign postirradiation stricture and (Stanton, Jr., and Jacox), 486
- Congenital atresia of upper two-thirds of vagina and cervical os with hematometra (Flemming and Kava), 296
 goiter (Parmelee, Allen, Stein, and Buxbaum), 145
 malformations (Murphy), 1067 (B. Rev.)
- Contraceptive practices (Kosmak), 652
- Cord, umbilical, prolapse of (Mengert and Longwell), 79
- Corpus luteum hormone effect of desoxycorticosterone (Hohlweg), 1084 (Abst.)
 hormonal treatment of uterine hyperkinesia with (Vautrin), 1084 (Abst.)
- Correspondence (Macklin), 540
- Cyclopropane anesthesia (Robbins), 1074 (B. Rev.)
- Cyst, residual, after hysterectomy (Hamant, Girard, and Soubiran), 539 (Abst.)
- Cystine, effect of, on human milk production (Daggs), 457
- Cystitis, catheter, prevention of postoperative traumatic and (Goodall and Quinn), 338
- D
- Dehydroisoandrosterone (Fluhmann), 613
- Deliveries, hospital, increase in (Plass), 659
- Delivery, pelvic operative, routine (Irving), 623
- Der Zyklus der Frau (Samuels), 1073 (B. Rev.)
- Dermoid, ovarian, containing teeth (Kronfeld), 466 (Abst.)
- Desoxycorticosterone and progesterone, absorption of (Warwick and Parkes), 1085 (Abst.)
 corpus luteum hormone effect of (Hohlweg), 1084 (Abst.)

In this series the systole is measured from the beginning of principal oscillations of the first sound, and when the auricular portion of the first sound appears in the presystolic area, it is not considered part of the ventricular systole.

As to the statement of Strassman and Mussey² that the rate of maternal and fetal hearts is in a ratio of 3:5 and 4:7, we must disagree, for the measurement of these heart rates taken simultaneously shows no rate relation between the two. For example, in one case the fetal heart rate is 163 and the mother's is 78, while in another, the fetal rate varies from 92 to 150 while the maternal rate remains at 82.

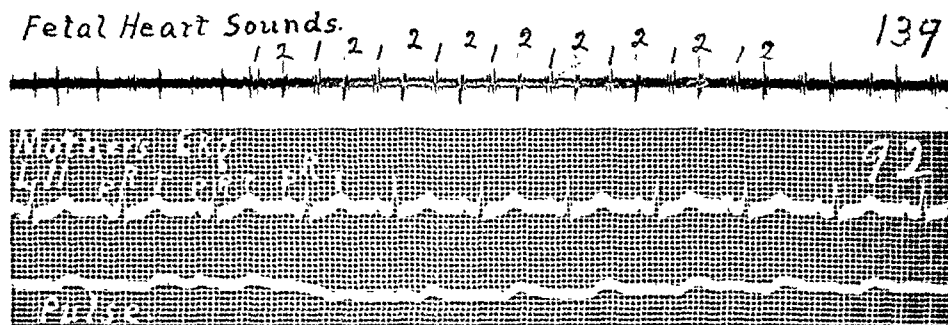


Fig. 5.—Rate 139. Intensity of the second (2) is very great (11 mm.) and the frequency is higher than that of the first (1). The amplitude is higher in the middle part. Vibrations of first 3 to 4 and second 4. Systole 0.20 to 0.22 second. Diastole 0.20 to 0.25 second. Mother's rate 92.

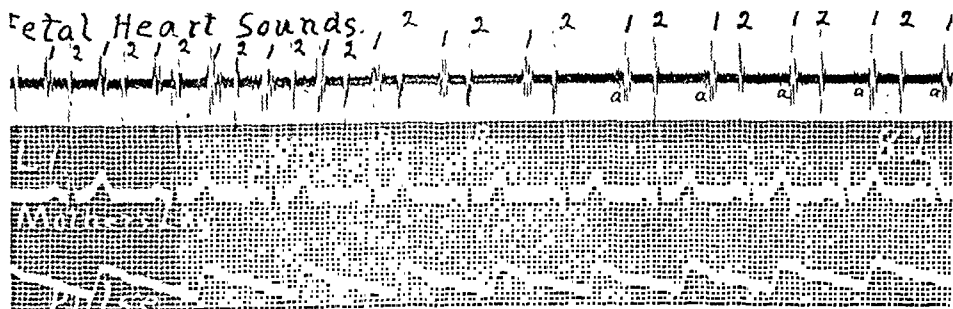


Fig. 6.—Rate 92-150. Amplitude of both sounds is very high, of the first (1) 21 mm. and second (2) 33.5 mm. As the rate decreases the auricular (a) part of the first sound advances into the presystolic area but the intensity of this sound is now lower. Vibrations first 1 to 8 and second sound 3 to 4. Systole 0.18 to 0.23 and diastole 0.23 to 0.53 second. Mother's rate 82.

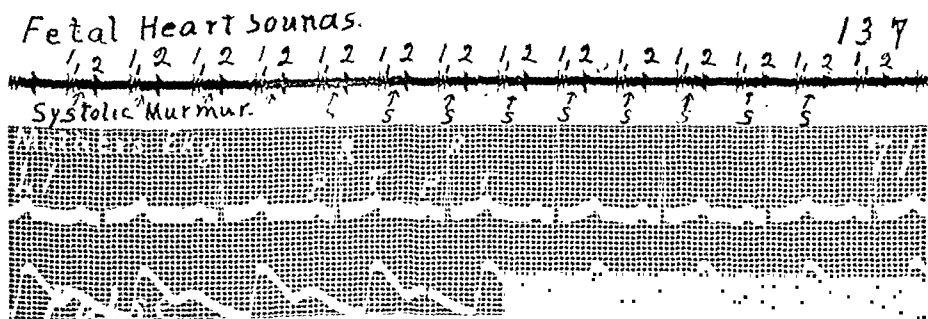


Fig. 7.—Rate 137. The second (2) is slightly greater in intensity than the first, which is split (1₁). The second part of the first sound is of low intensity and frequency, and this is followed immediately by a systolic murmur (*S*) of high frequency which continues into the second sound. Systole 0.17 to 0.19 and diastole, which is normal, 0.24 to 0.25 second in duration. Mother's heart rate 71.

Fetal—Cont'd

- mortality, effect of antenatal antisyphilitic therapy on, and on congenital syphilis, evaluation of (Dill, Stander, and Isenhour), 965
- Fever therapy and pregnancy (Marx), 1056
- Fibroids of uterus (Kanter and Klawans), 172 (Abst.)
uterine, need not be operated upon routinely (Vanverts), 173 (Abst.)
treatment of, new (Langlois), 172 (Abst.)
- Fibroma, bilateral, of ovaries combined with degenerating adenoma of right breast (Haumeder), 514
of ovary with ascites and hydrothorax (Bomze and Kirshbaum), 281
uterine, connection between, and hyperfolliculinemia (Portes), 172 (Abst.)
hysterectomy for, high partial (Azevedo and Dutra), 173 (Abst.)
- Fibromyoma angiomatosus of uterus (Gardner), 822
cervical, coexistence of, unusual, and squamous cell carcinoma (Dockerty and Masson), 477
of uterine cervix, pedunculated and expelled from vagina (Torpin and Beard), 490
- Film scales for use in pelvimetric roentgenography (Jacobs), 150
- Folliculin psychoses and circulatory disturbances (Baruk, David, Racine, and Mlle. Leuret), 1078 (Abst.)
quantitative analysis of, as basis of clinical and therapeutic orientation in gynecology (Ramos), 1078 (Abst.)
- Forceps, new (Luikart), 1058
- Friedman test, correlation of, and phase of endometrium in ectopic pregnancy (Goldblatt and Schwartz), 233
- Functional ovarian failure, endocrine therapy of (Hamblen), 615

G

- Genital carcinoma, pain in, treatment of, subarachnoid injection of alcohol for (Bauer), 278
- Genitalia, internal, tumors of, among prepubertal girls (Delannoy and Demarez), 139 (Abst.)
- Glands, adrenal and thyroid, relationship of, to toxemias of pregnancy (Hughes), 48
- Glycogen content of vaginal epithelium in children (Herrnberger and Horstmann), 110 (Abst.)
- Goiter, congenital (Parmelee, Allen, Stein, and Buxbaum), 145
- Gonadin (Erving, Sears, and Rock), 695
- Gonadotropic hormones (Fluhmann), 609;
(Heller and Heller), 1079 (Abst.)
equine, biologic characteristics of (Fluhmann), 1080 (Abst.)
clinical experiences with (Erving, Sears, and Rock), 695
in pregnancy, estrogenic and chorionic (Sieglar), 358 (Abst.)
therapeutic results from, clinical use and (Contamin and Lerailliez), 1079 (Abst.)
therapy, cyclic (Hamblen), 619
- Gonadotropins, chorionic (Hamblen), 616
equine (Hamblen), 616
pituitary (Hamblen), 616
- Gräfenburg ring, removal of, without interruption of pregnancy (Kimbrough, Jr., and Tompkins), 156

- Granulosa cell tumor, extraovarian (Powell and Black), 318
intraligamentous (Ragins and Frankel), 302
of ovary with hemoperitoneum and hemothorax (Vogt), 285
with precocious sexual development in child aged six (Stabler and Thomson), 1077 (Abst.)
- Grundlagen der Schwangerschaften-Ernaehrung (Gaetgens), 1068 (B. Rev.)
- Gynecologic operations, 534 (Absts.)
and their topographic-anatomic fundamentals (Martius), 1061 (B. Rev.)
practice, androgenic therapy in, evaluation of (Huffman), 675
- Gynecology, 1061 (B. Revs.)
and obstetrics, 1062 (B. Rev.)
practical problems in, department of, 158, 517
textbook of, combined (Kerr, et al.), 1064 (B. Rev.)
food factors, in accessory, importance of (Gaetgens), 47 (Abst.)
hormonal actions in, temperature curve and (Mocquot and Palmer), 1076 (Abst.)
hormone in, male, place of (Pierra and Erlande), 1086 (Abst.)
office (Greenhill), 1061 (B. Rev.)
radium therapy in (Ward), 158
sulfanilamide in, use of, and obstetrics (Gordon and Rosenthal), 211
textbook of (Young), 1061 (B. Rev.)
trends in, certain outstanding, during past forty years (Frank), 574

H

- Headaches, explanation for, which occur after spinal anesthesia (Vrba), 512 (Abst.)
- Heart, arrhythmias, fetal, due to anoxia, recognition and treatment of (Lund), 946
fetal, rate during pregnancy, normal variations of (Sontag and Newbery), 449
sounds, fetal, method for recording and reproducing (Smith and Hervert), 102
- Helium and oxygen, use of, in treatment of asphyxia neonatorum (Kane), 140
- Hematoma, traumatic, of omental adhesions simulating premature separation of placenta (Zupp and Mayer), 513
- Hematometra, homolateral, and hematosalpinx in uterus duplex (Arenas and Echegaray), 147 (Abst.)
with congenital atresia of upper two-thirds of vagina and cervical os (Flemming and Kava), 296
- Hemoperitoneum and hemothorax, granulosa cell tumor of ovary with (Vogt), 285
- Hemorrhage, functional (Ward), 160
- Hemorrhagic disease of newborn, intrauterine onset of (Javert), 453
- Hemothorax and hemoperitoneum, granulosa cell tumor of ovary with (Vogt), 285
- Hexoestrol, estrogenic properties of, and stilbestrol dipropionate (Bishop et al.), 1083 (Abst.)
- Histamine, injection of, local, treatment of pruritus vulvae by (Pagniez), 16
- Histology, textbook of (Jordan), 1070 (B. Rev.)
- Hormonal actions in gynecology, temperature curve and (Mocquot and Palmer), 1076 (Abst.)

- Diarrhea, epidemic infectious, of newborn infant (Cron, Shutter, and Lahmann), 88
- Dictionary, medical, practical (Stedman and Garber), 1073 (B. Rev.)
- Die Geburtsschilflichen Operationen (Marius), 1067 (B. Rev.)
- Die Krankhaften Psychischen Störungen der Rueckwandlungs-Jahre (Kehrer), 1073 (B. Rev.)
- Diet in pregnancy (Nixon), 357 (Abst.)
- Diethylstilbestrol (Huet, Comte, and Hershberg), 1082 (Abst.)
- clinical experience with (Felding and Möller-Christensen), 1083 (Abst.)
- effects of, on puerperal women, clinical study of (Connally, Jr., Dann, Reese, and Douglass), 445
- therapeutic properties of (Lorenzetti), 1083 (Abst.)
- Dysmenorrhea, endocrine therapy of (Varangot), 1080 (Abst.)
- testosterone propionate in, and functional uterine bleeding (Rubinstein), 1086 (Abst.)

E

- Eclampsia, effect of estrogens on true pre-eclampsia and (Shute and Barrie), 1003
- Ectopic pregnancy, endometrium in, phase of, correlation of Friedman test and (Goldblatt and Schwartz), 233
- El Diagnostico Precoz Del Embaraso (Laforet), 1068 (B. Rev.)
- Embolism and thrombosis, postoperative, prevention of (Schmid), 539 (Abst.)
- during hysterosalpingography with lipiodol, question of (Walther), 919 (Abst.)
- Embryologic research, changes in trend of (Streeter), 626
- Endocrine secretions, ovarian, disturbances of, asthma and (Chiray, Mollard, and Duret), 1079 (Abst.)
- studies of reproduction, twenty years of progress in (Fluhmann), 609
- therapy of dysmenorrheas (Varangot), 1080 (Abst.)
- of functional ovarian failure (Hamblen), 615
- Endocrinology, 1076 (Absts.)
- Endogene Endokrinotherapie in der Gynaekologie (Samuels), 1073 (B. Rev.)
- Endometrioma and myoma, 172 (Absts.)
- with pregnancy reaction (Holtz), 175 (Abst.)
- Endometriosis (Dougal), 173; (Heynemann), 174 (Absts.)
- of extremities (Navratil), 176 (Abst.)
- of lungs (Hobbs and Bortnick), 832; 175 (Abst.)
- pelvic (Henderson), 175 (Abst.)
- peritoneal, development of implantation theory for origin of (Sampson), 549
- Endometrium, tuberculosis of, coincidence of, with tuberculosis of lung (Lackner, Schiller, and Tulskey), 429
- like mucosa lining Fallopian tube (Marchetti), 69
- Equine gonadotropic hormone, clinical experiences with (Erving, Sears, and Rock), 695
- gonadotropins (Hamblen), 616
- Ergonovine, prophylactic use of, reduction of post-partum morbidity by (Lounsbury), 111
- Ergotrate (Lounsbury), 111
- Erythroblastosis fetalis (Wolfe and Neigus), 31

- Estradiol (Fluhmann), 612
- and estrone, implantation of tablets of, depression of hypophyseal activity by (Deanesly), 1081 (Abst.)
- benzoate, activity of, vitamins A and C, and diethylstilbestrol in experimental fibromatosis (Moricaud and Simard), 1081 (Abst.)
- effects of, upon lactation (Abarbanel and Goodfriend), 1038
- Estrin, attempted induction of labor with, results of (Lubin and Waltman), 358 (Abst.)
- influence of, on vaginal epithelium of young girls (Herrnberger), 1081 (Abst.)
- Estriol (Fluhmann), 612
- Estrogenic and chorionic gonadotropic hormone in pregnancy (Siegler), 358 (Abst.)
- hormones (Fluhmann), 611
- in treatment of infant vulvovaginitis (Weed and Collins), 1082 (Abst.)
- Estrogens (Hamblen), 617
- during menopause, psychiatric contraindications in use of (Heavener), 980
- effect of, on true pre-eclampsia and eclampsia (Shute and Barrie), 1003
- on urinary volume (Sharpey-Schafer and Schrire), 1081 (Abst.)
- therapeutic, evaluation of stilbestrol as (Salmon, Geist, and Walter), 243
- Estrone (Fluhmann), 612
- and estradiol, implantation of tablets of, depression of hypophyseal activity by (Deanesly), 1081 (Abst.)
- effects of, upon lactation (Abarbanel and Goodfriend), 1038
- Examination, premarital, laws in operation (Edwards), 428 (Abst.)
- Expectant motherhood (Eastman), 1069 (B. Rev.)
- Extraovarian granulosa cell tumor (Powell and Black), 318

F

- Fallopian tube, cancer of, primary (Martzloff), 804
- closed, occlusive action of lipiodol on (Held), 918 (Abst.)
- endometrium-like mucosa lining (Marchetti), 69
- prolapse and torsion of right, with vaginal bleeding, following vaginal hysterectomy (Bower and Pearce), 1047
- torsion and prolapse of right, with vaginal bleeding, following vaginal hysterectomy (Bower and Pearce), 1047
- Feldman adaptometer (Hirst and Shoemaker), 12
- Fertility, relation of certain seminal findings to (Moench), 921 (Abst.)
- Fetal and maternal polypitidemia (Cetrioni), 356 (Abst.)
- and neonatal death (Potter and Adair), 1065 (B. Rev.)
- ascites, obstructed labor due to (Ellison), 1057
- heart arrhythmias due to anoxia, recognition and treatment of (Lund), 946
- rate during pregnancy, normal variations of (Sontag and Newbery), 449
- sounds, method for recording and reproducing (Smith and Hervert), 102

Labor—Cont'd

- effect of salt poor diet during pregnancy upon duration of (Pomerance and Daichman), 463
- induction of, attempted, with estrin, results of (Lubin and Waltman), 358 (Abst.)
- obstructed, due to fetal ascites (Ellison), 1057
- paraldehyde in blood following its administration during, concentration (Gardner, Levine, and Bodansky), 435
- uterine motility during, mechanical ink writing recorder suitable for recording, and pregnancy (Fenning), 330
- vitamin K, effect of, administered to patients in (Fitzgerald and Webster), 413
- Lactation, effect of prolactin on, in nursing women (Kenny and King), 1086 (Abst.)
 - of stilbestrol upon (Abarbanel and Goodfriend), 1037
 - inhibition of, post partum with testosterone propionate (Beilly and Solomon), 1085 (Abst.)
 - metabolism in, calcium, phosphorus and nitrogen, in women during second half of pregnancy and in early (Oberst and Plass), 399
 - suppression of, by stilbestrol (Mucklé), 133
- Lactogenic hormone (Fluhmann), 610
- Lead mobilization accompanying toxemia of pregnancy (Letonoff, Reinhold, Riggs, and Cohn), 1017
- Leucoplakia-kraurosis vulvae as cause of intractable pruritus, tattooing (puncturation) with mercury sulfide for treatment of (Turrell), 334
- Ligaments, round, reduction and attachment of, operation for uterine retrodisplacement and prolapse by (Taylor), 1026
- Lipiodol, fluid, hysterosalpingography (Palmer, Pulsford, and Christeas), 918 (Abst.)
 - occlusive action of, on closed Fallopian tubes (Held), 918 (Abst.)
- Lipoma of uterus (Ritter and Stringer), 501
- Liver, detoxicating function of, during puerperal state (Bortolucci), 355 (Abst.)
- Louisville Obstetrical and Gynecological Society, officers of, 179, 725
- Lungs, endometriosis of (Hobbs and Bortnick), 832; (Hobbs and Bortnick), 175 (Abst.)
 - tuberculosis of, coincidence of tuberculosis of endometrium with (Lackner, Schiller, and Tulskey), 429
- M
- Malformations, congenital (Murphy), 1067 (B. Rev.)
- Manikin, obstetrical practice (McNeile), 1066 (B. Rev.)
- Marriage, sex in (Groves and Groves), 1072 (B. Rev.)
- Marrow, sternal, hematology of, and venous blood of pregnant and nonpregnant women (Pitts and Packham), 355 (Abst.)
- Maternal welfare activities, development of (Adair), 633
 - department of, 347, 526
- Medical dictionary, practical (Stedman and Garber), 1073 (B. Rev.)
 - mycology, introduction to (Lewis and Hopper), 1074 (B. Rev.)
 - practice, specialties in (van Nuys-Allen), 1069 (B. Rev.)

- Megalothymia, prepubertal (Turpin, Chasagne, and Lefebvre), 1077 (Abst.)
- Membranes, rupture of, premature elective (Keettel, Diddle, and Plass), 225
- Menometrorrhagia, functional, diagnosis and treatment of, in adolescence (Kreis), 329 (Abst.)
- Menopausal symptoms, treatment of stilbestrol in (Payne and Mucklé), 135
- Menopause, artificial, produced by roentgen rays, hormonal studies in (Nathanson, Rice, and Meigs), 936
 - estrogens during, psychiatric contraindications in use of (Heaver), 980
 - management of (Novak), 589
- Menstrual cycle (Fluhmann), 613
 - hormone excretion during, further studies on (D'Amour), 958
 - urinary prolan excretion during (Bagby), 1079 (Abst.)
- Metabolism, calcium, phosphorus and nitrogen, in women during second half of pregnancy and in early lactation (Oberst and Plass), 399
- Michigan Society of Obstetricians and Gynecologists, officers of, 726
- Midwifery, pictorial (Berkeley), 1068 (B. Rev.)
- Mikulicz drainage in treatment of tuberculous salpingitis (Lapeyre, Estor, and Gros), 537 (Abst.)
- Milk, human, production, effect of cystine on (Daggs), 457
- Mongolism, time and stage in development at which factors operate to produce (Southwick), 1021 (Abst.)
- Monster, amorphous, difficult labor due to (Le Vine and Wolf), 327
- Morbidity, post-partum, reduction of, by prophylactic use of ergonovine (Lounsbury), 111
- Motherhood, expectant (Eastman), 1069 (B. Rev.)
- Mucosa, endometrium-like, lining Fallopian tube (Marchetti), 69
- Muscle, serratus anterior, isolated paralysis of, during puerperium (McGoogan), 313
- Mycology, medical, introduction to (Lewis and Hopper), 1074 (B. Rev.)
- Mycosis, vulval and vaginal, and trichomoniasis (Hesseltine), 641
- Myoma and endometrioma, 172 (Absts.)
 - of vagina (DaCosta), 172 (Abst.)
 - submucous (Kangas), 173 (Abst.)
- Myxosarcoma, congenital, of labium majus, complicating congenital atresia of tricuspid valve (Amolsch), 149 (Abst.)

N

- Narcosis, intravenous, in obstetrics (Kirchner), 1060 (Abst.)
- Nausea and vomiting of pregnancy due to allergic reaction (Finch), 1029
- Neonatal and fetal death (Potter and Adair), 1065 (B. Rev.)
 - deaths and stillbirths (Runnels and Wylie), 526
 - period, ascorbic acid in (Elmby and Christensen), 356 (Abst.)
- Nephritis, chronic, and pregnancy fatalities in Philadelphia (Paxson), 995
- New England Obstetrical and Gynecological Society, officers of, 180, 726
- New Orleans Obstetrical and Gynecological Society, officers of, 180, 726
- New York Obstetrical Society, officers of, 179, 725
 - transactions of, 170, 352

Hormonal—Cont'd

- studies in artificial menopause produced by roentgen rays (Nathanson, Rice, and Meigs), 936
- Hormones, androgenic (Fluhmann), 613
- corpus luteum, effect of desoxycorticosterone (Hohlweg), 1084 (Abst.)
- estrogenic (Fluhmann), 611
- in treatment of infant vulvovaginitis (Weed and Collins), 1082 (Abst.)
- excretion during menstrual cycle, further studies on (D'Amour), 958
- follicular, tumorigenic powers of stilbestrol and (Lipschutz and Vargas), 1084 (Abst.)
- gonadotropic (Fluhmann), 609; (Heller and Heller), 1079 (Abst.)
- equine, biologic characteristics of (Fluhmann), 1080 (Abst.)
- clinical experiences with (Erving, Sears, and Rock), 695
- lactogenic (Fluhmann), 610
- male, in gynecology (Pierra and Erlande), 1086 (Abst.)
- sex, absence of, acute effects of (Dick and Hooker), 1080 (Abst.)
- Hospital deliveries, increase in (Plass), 659
- small, as obstetric hazard (Runnels), 347
- statistics, evaluation of (Ward), 655
- Hydrops fetalis (Wolfe and Neigus), 31
- Hydrothorax and ascites, fibroma of ovary with (Bomze and Kirshbaum), 281
- Hyperfolliculinemia, connection between uterine fibromas and (Portes), 172 (Abst.)
- secondary tetany from (Maranon, Richet, Pergola, and Lesueur), 1078 (Abst.)
- Hypertension and renal damage, pregnancy pyelonephritis in relation to (Crabtree and Reid), 17
- Hypertrophy, cardiac, during pregnancy, question of (VanLiere and Sleeth), 355 (Abst.)
- Hypophyseal activity, depression of, by implantation of tablets of estrone and estradiol (Deanesly), 1081 (Abst.)
- Hypothyroid and normal females, effect of thyroid on sterility in (Winkelstein), 94
- Hysterectomies, analysis of 300 (Ashton), 123
- complications of, postoperative (Ashton), 126
- high partial, for uterine fibroma (Azevedo and Dutra), 173 (Abst.)
- indications for (Ashton), 125
- morbidity in (Ashton), 125
- mortality in (Ashton), 127
- residual cysts after (Hamant, Girard, and Soubiran), 539 (Abst.)
- rupture of vaginal scar after (Thalheimer and Contiades), 537 (Abst.)
- study of 1,200 cases of (Smith), 118
- supravaginal, carcinoma of cervix after (Behney), 780
- total (Radford), 534 (Abst.)
- vaginal (Faure), 534 (Abst.)
- followed by prolapse and torsion of right Fallopiian tube with vaginal bleeding (Bower and Pearce), 1047
- reflections on (Chavannaz), 534 (Abst.)
- Hysteropexy, new technique of (Malfanti), 538 (Abst.)
- Hysterosalpingography with fluid lipiodol (Palmer, Pulsford, and Christeas), 918 (Abst.)
- with lipiodol, embolism during, question of (Walther), 919 (Abst.)

I

- Icterus gravis, maternal findings in (Wolfe and Neigus), 40
- neonatorum (Wolfe and Neigus), 38
- newborn infants with, findings in (Wolfe and Neigus), 41
- Il Ciclo Sessuale della Madri delle famiglie Numerose, 1068 (B. Rev.)
- Implantation theory, development of, for origin of peritoneal endometriosis (Sampson), 549
- Incontinence, urinary, stress of, method for evaluating (Barnes), 381
- Infant, newborn, epidemic infectious diarrhea of (Cron, Shutter, and Lahmann), 88
- prothrombin concentration in parturient women and their (Javert and Moore), 1022
- Infection, presence of, management of adherent placenta in (Wilson), 854
- puerperal (Watson), 584
- Infertility and sterility (Stein), 918 (Abst.)
- Infrared photography, study of superficial venous pattern in pregnant and nonpregnant women by (Gorman and Hirsheimer), 354 (Abst.)
- Insufficiency, renal, following transfusion of compatible blood (Brainard), 142
- suprarenal, complicating pregnancy, acute crisis of (Galloway, Sutton, and Ashworth), 148
- Insufflation, uterotubal, as test for tubal patency, 1920-1940 (Rubin), 628
- Intestinal obstruction, acute, complicating pregnancy and post-partum period (Weintraub and Jaffe), 481
- due to malignancy complicating pregnancy (DerBrucke), 307
- Intraligamentous granulosa cell tumor (Ragins and Frankel), 302
- Intrauterine onset of hemorrhagic disease of newborn (Javert), 453
- pregnancy, simultaneous ovarian and (Milnor and Bowles), 511
- Inversion, acute, of uterus post partum associated with placenta accreta (Halpert and Graffagnino), 509
- Item, American Board of Obstetrics and Gynecology, Inc., 176, 360, 544, 924, 1087
- College of Surgeons, obstetrics and gynecology in graduate training program of, 541
- Central Association of Obstetricians and Gynecologists, 544
- Obstetrics and Gynecology in graduate training program of American College of Surgeons, 541

K

- Kidney, ectopic and renal tumor, associating or simulating uterine and adnexal tumor (Rubin), 536

L

- La Radiologia en Obstetricia (Leon), 1065 (B. Rev.)
- Labor and pregnancy, artificial termination of, modern trends in (Irving), 621
- ascorbic acid in (Elmby and Christensen), 356 (Abst.)
- complicated by Brenner tumor of ovary (Siegel), 337
- by spontaneous rupture of spleen (Shannon), 323
- difficult, due to amorphous monster (Le Vine and Wolf), 327

- Pelvimetry, roentgen, as routine prenatal procedure (Thoms), 891
- Pelvis, female, purulent accumulations in simple puncture as palliative therapeutic treatment in (Von Mihalkovics), 536 (Abst.)
- Perineal anesthesia and paraldehyde analgesia in obstetrics (Fraser and Jones), 506
- endometriosis, development of implantation theory for origin of (Sampson), 549
- Peritonitis of pelvic origin, new phenomenon which is accurate indication for surgical interference in (Knaus), 539 (Abst.)
- Phosphatase during puerperium (Quinto), 356 (Abst.)
- Phosphorus metabolism, calcium and nitrogen, in women during second half of pregnancy and in early lactation (Oberst and Plass), 399
- Pittsburgh Obstetrical and Gynecological Society, officers of, 179, 725
- transactions of, 171, 352
- Pituitary gland, comparative anatomy and pharmacology of, of unusual "experimental" animals (Geiling), 727
- gonadotropins (Hamblen), 616
- Pituitrin (Lounsbury), 111
- Placenta accreta associated with acute inversion of uterus post partum (Halpert and Graffagnino), 509
- adherent, management of, in presence of infection (Wilson), 854
- chorioangioma of (Fisher), 493
- premature separation, traumatic hematoma of omental adhesions simulating (Zupp and Mayer), 513
- roentgen visualization of, by soft tissue technique (Dippel and Brown), 986
- Placental blood, preservation of, studies on (Scudder, Drew, and Damon), 461
- Polypitidemia, fetal and maternal (Cetrioni), 356 (Abst.)
- Portland Society of Obstetrics and Gynecology, officers of, 179, 725
- Posterior-pituitary extract, response of non-gravid human uterus to, and its fractions oxytocin and vasopressin (McLellan), 1084 (Abst.)
- Pre-eclampsia, effect of estrogens on, and eclampsia (Shute and Barrie), 1003
- treatment of (Anderson), 517
- Pregnancies, tubal, successive, coexistent (Behney and Hanes), 155
- Pregnancy, abdominal (Lull), 194
- and disease (Ehrenfest), 596
- and fever therapy (Marx), 1056
- and labor, artificial termination of, modern trends in (Irving), 621
- ascorbic acid in, labor, puerperium and neonatal period (Elmby and Christensen), 356 (Abst.)
- blood in, composition of (Ramsay, Thierens, and Magee), 355 (Abst.)
- cardiac hypertrophy during, question of (VanLiere and Sleeth), 355 (Abst.)
- complicated by intestinal obstruction, acute, and post-partum period (Weintraub and Jaffe), 481
- by suprarenal insufficiency, acute crisis of (Galloway, Sutton, and Ashworth), 148
- by tuboovarian abscess (Brougher), 1053
- diet in (Nixon), 357 (Abst.)
- Pregnancy—Cont'd
- duration of, and its seasonal influences (Bernhart), 359 (Abst.)
- calculation of (Wiessman), 359 (Abst.)
- ectopic, endometrium in, phase of, correlation of Friedman test and (Goldblatt and Schwartz), 233
- estrogenic and chorionic gonadotropic hormone in (Siegler), 358 (Abst.)
- fatalities and chronic nephritis in Philadelphia (Paxson), 995
- fetal heart rate during, normal variations of (Sontag and Newbery), 449
- interruption of, relation between elimination of ascorbic acid in urine and (Grossi), 357 (Abst.)
- malignancy complicating, intestinal obstruction due to (DerBrucke), 307
- metabolism in, calcium, phosphorus and nitrogen, in women during second half of, and in early lactation (Oberst and Plass), 399
- nausea and vomiting of, due to allergic reaction (Finch), 1029
- nutrition study in (Williams, Hark, and Fralin), 1
- ovarian and intrauterine, simultaneous (Milnor and Bowles), 511
- physiology of, 353 (Absts.)
- prolonged, or late fecundation (Kreis), 359 (Abst.)
- pyelonephritis in relation to renal damage and hypertension (Crabtree and Reid), 17
- reaction, endometrioma with (Holtz), 175 (Abst.)
- relations between ocular tension and (Patat), 355 (Abst.)
- retrodisplacement of uterus in relation to (Aldridge), 361
- salt poor diet during, effect of, upon duration of labor (Pomerance and Daichman), 463
- test for, cold pressor (Chesley and Chesley), 353
- Hogben, biologic determination of (Laves), 354 (Abst.)
- intradermal, evaluation of (Parsons), 353 (Abst.)
- of Nito (Martzky and Pap), 353 (Abst.)
- toxemia of, lead mobilization accompanying (Letonoff, Reinhold, Riggs, and Cohn), 1017
- relationship of thyroid and adrenal glands to (Hughes), 48
- tubal, associated with tubal tuberculosis (Bland), 271
- bilateral simultaneous (Lee and Stone), 316
- tuberculin test in, significance of (Maeder and Myers), 218
- uterine bleeding in last trimester of (Wallace), 128
- motility during, mechanical ink writing recorder suitable for recording, and labor (Penning), 330
- vitamin A in (Hirst and Shoemaker), 12
- content in (Williams, Hark, and Fralin), 1
- vomiting and nausea of, due to allergic reaction (Finch), 1029
- Pregnanediol (Fluhmann), 613
- determination as an aid in clinical diagnosis (Buxton), 202
- Pregneninolone (Fluhmann), 613
- oral, laboratory and clinical experience with (Cohen and Stein), 713
- Premarital examination laws in operation (Edwards), 428 (Abst.)

- Newborn child, on inheritance of parents' constitution by (Ritala), 945 (Abst.)
 hemorrhagic disease of, intrauterine onset of (Javert), 453
 infant, epidemic infectious diarrhea of (Cron, Shutter, and Lahmann), 88
 Nicolas-Favre disease in gynecology and obstetrics (Vignes), 157 (Abst.)
 Nicotine and cigarette smoke, effects of, on pregnant albino rats and their offspring (Essenberg, Schwind, and Patras), 380 (Abst.)
 Nitrogen metabolism, calcium and phosphorus, in women during second half of pregnancy and in early lactation (Oberst and Plass), 399
 Nursing, public health, manual of, 1071 (B. Rev.)
 Nutrition study in pregnancy (Williams, Hark, and Fralin), 1

O

- Obstetric complications to sterility, relation of (Nicholls), 276
 difficulties, management of (Titus), 1064 (B. Rev.)
 hazard, small hospital as (Runnels), 347
 Society of Syracuse Hospitals, officers of, 726
 Obstetrical manikin practice (McNeile), 1066 (B. Rev.)
 practice (Beck), 1065 (B. Rev.)
 Society of Boston, officers of, 179, 725
 transactions of, 171
 of Philadelphia, officers of, 179, 725
 transactions of, 170
 Obstetricia normal (Briquet), 1066 (B. Rev.)
 Obstetrics, 1062 (B. Revs.)
 and gynecology, 1062 (B. Rev.)
 department of practical problems, 158, 517
 textbook of, combined (Kerr, et al.), 1064 (B. Rev.)
 food factors (vitamins) in, accessory, importance of (Gaetgens), 47 (Abst.)
 narcosis in, intravenous (Kirchner), 1060 (Abst.)
 paraldehyde analgesia and perineal anesthesia (Fraser and Jones), 506
 practical teaching in, application of sculpture to (Dickinson), 662
 sulfanilamide in, use of, and gynecology (Gordon and Rosenthal), 211
 synopsis of (Litzenberg), 1067 (B. Rev.)
 vitamin K in (Hellman, Shettles, and Eastman), 844
 Obstruction, intestinal, acute, complicating pregnancy and post-partum period (Weintraub and Jaffe), 481
 due to malignancy complicating pregnancy (DerBrucke), 307
 Ocular tension, relations between, and pregnancy (Patat), 355 (Abst.)
 Office gynecology (Greenhill), 1061 (B. Rev.)
 Oliguria and anuria, treatment of (Dieckmann and Kramer), 61
 Oophoritis, sclerocystic, conservative surgery for, results of (Decoux and Patoir), 539 (Abst.)
 Operation, Baldy-Webster, by vaginal route (Barros), 537 (Abst.)
 for uterine retrodisplacement and prolapse by reduction and attachment of round ligaments (Taylor), 1026
 Operation—Cont'd
 gynecologic, 534 (Absts.)
 and their topographic-anatomic fundamentals (Martius), 1061 (B. Rev.)
 lower segment, cesarean section (Marshall), 1066 (B. Rev.)
 surgical, atlas of (Cutler), 1069 (B. Rev.)
 Operative surgery, synopsis of (Mobley), 1075 (B. Rev.)
 Ovarian and intrauterine pregnancy, simultaneous (Milnor and Bowles), 511
 dermoid containing teeth (Kronfeld), 466 (Abst.)
 endocrine secretions, disturbances of, and asthma (Chiray, Mollard, and Duret), 1079 (Abst.)
 failure, functional, endocrine therapy of (Hamblen), 615
 tumors, changing conceptions of (Taylor, Jr.), 566
 Ovaries, fibroma of, bilateral, combined with degenerating adenoma of right breast (Haumeder), 514
 Ovary, Brenner tumor of, complicating labor (Siegel), 337
 carcinoma of (Pemberton), 751
 fibroma of, with ascites and hydrothorax (Bomze and Kirshbaum), 281
 granulosa cell tumor of, with hemoperitoneum and hemothorax (Vogt), 285
 Ovulation, ensemble for (Dickinson), 921 (Abst.)
 Ovum, human, endouterine nidation of, anatomic report in favor of (D'Erchia), 354 (Abst.)
 Oxygen and helium, use of, in treatment of asphyxia neonatorum (Kane), 140

P

- Pacific Coast Obstetrical and Gynecological Society, officers of, 180, 726
 Pain in genital carcinoma, treatment of, subarachnoid injection of alcohol for (Bauer), 278
 intractable, cobra venom for (Kelso), 1050
 relief of, in carcinoma of cervix uteri (Todd), 492 (Abst.)
 Paraldehyde analgesia and perineal anesthesia in obstetrics (Fraser and Jones), 506
 concentration of, in blood following its administration during labor (Gardner, Levine, and Bodansky), 435
 rectal administration of, technique for (Kotz and Kaufman), 332
 Paralysis, isolated, of serratus anterior muscle during puerperium (McGoogan), 313
 Parturient women, prothrombin concentration in, and their newborn infants (Javert and Moore), 1022
 Pelvic architecture, more recent conceptions of (Caldwell, Moloy, and D'Esopo), 558
 capacity, estimation of (Thoms), 1067 (B. Rev.)
 depth, accurate roentgenologic method for determining (Arnell, Guerriero, and Irwin), 467
 endometriosis (Henderson), 175 (Abst.)
 puncture (Schultz), 535 (Abst.)
 structures, female, altered mechanics of (Beasley), 537 (Abst.)
 tuberculosis (Lahmann and Schwartz), 439
 Pelvimetric roentgenography, film scales for use in (Jacobs), 150

- Sexual pathology (Hirschfeld), 1072 (B. Rev.)
- Shock: blood studies as guide to therapy (Scudder), 1073 (B. Rev.)
- Society transactions, Brooklyn Gynecological Society, 171
- Chicago Gynecological Society, 170, 171, 533, 724
- New York Obstetrical Society, 170, 352
- Obstetrical Society of Boston, 171 of Philadelphia, 170
- Pittsburgh Obstetrical and Gynecological Society, 171, 352
- South Atlantic Association of Obstetricians and Gynecologists, 171
- South Atlantic Association of Obstetricians and Gynecologists, officers of, 179, 725
- transactions of, 171
- Sperm immunity in rat (Eastman, Guttmacher, and Stewart), 921 (Abst.)
- motility, relation of, to fertilizing ability (Williams), 919 (Abst.)
- Spermatozoa, biologic action of cervical and vaginal secretions on, association between (Laffont and Bourgarel), 920 (Abst.)
- vitality of, effect of cervical secretions on (Watson), 920 (Abst.)
- Spleen, rupture of, spontaneous, complicating labor (Shannon), 323
- Squamous cell carcinoma, coexistence of, unusual, and cervical fibromyoma (Dockerty and Masson), 477
- of uterus, mixed adenocarcinoma and (Skinner and McDonald), 258
- Sterility (Erving, Sears, and Rock), 703; 918 (Absts.)
- and infertility (Stein), 918 (Abst.)
- and pH of masculine and feminine secretions (Laffont and Bourgarel), 919 (Abst.)
- effect of thyroid on, in normal and hypothyroid females (Winkelstein), 94
- effective therapy in, etiology and basis of (Berutti), 923 (Abst.)
- obstetric complications to, relation of (Nicholls), 276
- radiology in (Robecchi), 922 (Abst.)
- treatment of (Glober), 922 (Abst.)
- salpingostomies (Villard), 922 (Abst.)
- tubal, treatment of, total linear salpingostomy for (Chalier), 921 (Abst.)
- Stilbestrol (Hamblen), 618
- and anhydro-oxyprogesterone (Wenner and Joel), 1083 (Abst.)
- dipropionate, estrogenic properties of, and hexoestrol (Bishop et al.), 1083 (Abst.)
- effects of, upon lactation (Abarbanel and Goodfriend), 1037
- evaluation of, as therapeutic estrogen (Salmon, Geist, and Walter), 243
- in treatment of menopausal symptoms (Payne and Mucklé), 135
- suppression of lactation by (Mucklé), 133
- tumorigenic powers of, and follicular hormones (Lipschutz and Vargas), 1084 (Abst.)
- Stillbirths and neonatal deaths (Runnels and Wylie), 526
- Stricture, postirradiation, benign, and primary carcinoma of colon (Stanton, Jr., and Jacox), 486
- Struma ovarii, functional and growth characteristics of (Emge), 738
- Subarachnoid injection of alcohol for treatment of pain in genital carcinoma (Bauer), 278
- Sulfamide powder, in local treatment of soft chancre and cutaneous pyoderma (Sezary), 193 (Abst.)
- Sulfanilamide in obstetrics and gynecology (Gordon and Rosenthal), 211
- therapy in treatment of febrile abortions (Mencken and Lansman), 1013
- Suprarenal insufficiency complicating pregnancy, acute crisis of (Galloway, Sutton, and Ashworth), 148
- Supravaginal hysterectomy, carcinoma of cervix after (Behney), 780
- Surgery, abdominal, gynecologic, method of getting patients out of bed early after (Charbonnier), 540 (Abst.)
- conservative, for sclerocystic oophoritis, results of (Decoulx and Patoir), 539 (Abst.)
- operative, synopsis of (Mobley), 1075 (B. Rev.)
- Surgical operations, atlas of (Cutler), 1069 (B. Rev.)
- Syphilis, congenital, effect of antenatal antisyphilitic therapy on fetal mortality and on, evaluation of, (Dill, Stander, and Isenhour), 965
- T
- Tattooing (puncturation) with mercury sulfide for treatment of intractable pruritus caused by leucoplakia-kraurosis vulvae (Turell), 334
- Test, cold pressor, in pregnancy (Chesley and Chesley), 353 (Abst.)
- for tubal patency, 1920-1940, uterotubal insufflation as (Rubin), 628
- Friedman, correlation of, and phase of endometrium in ectopic pregnancy (Goldblatt and Schwartz), 233
- Hogben, for pregnancy, biologic determination of (Laves), 354 (Abst.)
- intra dermal, for pregnancy, evaluation of (Parsons), 353 (Abst.)
- pregnancy, of Nito (Martzy and Pap), 353 (Abst.)
- tuberculin, in pregnancy, significance of (Maeder and Myers), 218
- Testosterone (Fluhmann), 613
- propionate (Huffman), 680
- in functional uterine bleeding and dysmenorrhea (Rubinstein), 1086 (Abst.)
- inhibition of lactation post partum with (Beilly and Solomon), 1085 (Abst.)
- Tetany, secondary, from hyperfolliculinemia (Maranon et al.), 1078 (Abst.)
- Texas Association of Obstetricians and Gynecologists, officers of, 180 726
- Thrombosis and embolism, postoperative, prevention of (Schmid), 539 (Abst.)
- Thyroid, effect of, on sterility in normal and hypothyroid females, (Winkelstein), 94
- glands, relationship of, and adrenal, to toxemias of pregnancy (Hughes), 48
- substance (Hamblen), 615
- Torsion, acute, of gravid uterus (Olivella and Feo), 1036 (Abst.)
- and prolapse of right Fallopian tube with vaginal bleeding, following vaginal hysterectomy (Bower and Pearce), 1047
- Toxemia of pregnancy, lead mobilization accompanying (Letonoff, Reinhold, Riggs, and Cohn), 1017
- relationship of thyroid and adrenal glands to (Hughes), 48

- Premature separation of placenta, traumatic hematoma of omental adhesions simulating (Zupp and Mayer), 513
- Presentation, impacted mentum posterior, pubiotomy (Sharkey), 267
- Presidential address at American Gynecological Society meeting (Adair), 925
- Primer Congreso Chileno y Americano de Cirurgia, 1071 (B. Rev.)
- Progesterone (Fluhmann), 612; (Hambelen), 617
and desoxycorticosterone, absorption of (Warwick and Parkes), 1085 (Abst.)
in troubles of nidation, results with (Vermelin), 1085 (Abst.)
uterine bleeding induced by (Zondek, Rozin, and Vesell), 391
- Progestin in obstetric complications, use of (Falls), 1085 (Abst.)
- Prolactin, effect of, on lactation in nursing women (Kenny and King), 1086 (Abst.)
on secretion of milk in women (Kajser), 1086 (Abst.)
- Prolan excretion, urinary, during menstrual cycle (Bagby), 1079 (Abst.)
- Prolapse and torsion of right Fallopian tube with vaginal bleeding, following vaginal hysterectomy (Bower and Pearce), 1047
of umbilical cord (Mengert and Longwell), 79
of vagina, reconstruction of round ligaments in correcting, ox fascia lata for (Ward), 538 (Abst.)
operation for uterine retrodisplacement and, by reduction and attachment of round ligaments (Taylor), 1026
- Prothrombin concentration in parturient women and their newborn infants (Javert and Moore), 1022
- Pruritus, intractable, caused by leucoplakia-kraurosis vulvae, tattooing (puncturation) with mercury sulfide for treatment of (Turell), 334
vulvae, treatment of, by local injections of histamine (Pagniez), 16 (Abst.)
- Pseudohermaphroditism (Pratt), 870
- Pubiotomy in impacted mentum posterior presentation (Sharkey), 267
- Public health nursing, manual of, 1071 (B. Rev.)
- Puerperal infection (Watson), 584
- Puerperium, ascorbutic acid in (Elmby and Christensen), 356 (Abst.)
isolated paralysis of serratus anterior muscle during (McGoogan), 313
phosphatase during (Quinto), 356 (Abst.)
- Puncture, simple, as palliative therapeutic treatment in purulent accumulations in female pelvis (von Mihalkevics), 536 (Abst.)
- Pyelonephritis, pregnancy, in relation to renal damage and hypertension (Crabtree and Reid), 17
- Pyosalpinx, treatment of (Haultain), 535 (Abst.)
- R**
- Radiology in female sterility (Robecchi), 922 (Abst.)
- Radiotherapy, complications of (Ward), 167
- Radium therapy in gynecology (Ward), 158
- Rectal administration of paraldehyde, technique for (Kotz and Kaufman), 332
- Renal agenesis, right uterus unicornis associated with (Schattenberg and Ziskind), 293
damage and hypertension, pregnancy pyelonephritis in relation to (Crabtree and Reid), 17
insufficiency following transfusion of compatible blood (Brainard), 142
- Reproduction, endocrine studies of, twenty years of progress in (Fluhmann), 609
- Reproductive cycle, relation of vitamin B₁ to (Williams, Griffith, and Franklin), 181
- Retractor, abdominal, weighted (Visser), 516
- Retrodisplacement of uterus in relation to pregnancy (Aldridge), 361
uterine, operation for, and prolapse by reduction and attachment of round ligaments (Taylor), 1026
- Reviews and abstracts, department of, 172, 353, 534, 918, 1076
- Ring, Gräfenburg, removal of, without interruption of pregnancy (Kimbrough, Jr., and Tompkins), 156
- Roentgen pelvimetry as routine prenatal procedure (Thoms), 891
rays, artificial menopause produced by, hormonal studies in (Nathanson, Rice, and Meigs), 936
visualization of placenta by soft tissue technique (Dippel and Brown), 986
- Roentgenography, pelvimetric, film scales for use in (Jacobs), 150
- Roentgenologic method for determining pelvic depth, an accurate (Arnell, Guerriero, and Irwin), 467
- Roster of American Obstetrical and Gynecological Societies, 179, 725
- Round ligaments, reconstruction of, in correcting prolapse of vagina, ox fascia lata for (Ward), 538 (Abst.)
- Rupture, premature elective, of membranes (Keettel, Diddle, and Plass), 225
of spleen, spontaneous, complicating labor (Shannon), 323
of vaginal scar after hysterectomy (Thalheimer and Contiades), 537 (Abst.)
- S**
- St. Louis Gynecological Society, officers of, 180, 726
- Salpingitis, tuberculous, treatment of, Mikulicz drainage in (Lapeyre, Estor, and Gros), 537 (Abst.)
- Salpingostomies in treatment of sterility (Villard), 922 (Abst.)
- Salpingostomy, total linear, for treatment of tubal sterility (Chalier), 921 (Abst.)
- Salt poor diet during pregnancy, effect of, upon duration of labor (Pomerance and Daichman), 463
- San Francisco Gynecological Society, officers of, 180, 726
- Scissors, new, for incising uterus in cesarean section (Cinberg), 336
- Sculpture, application of, to practical teaching in obstetrics (Dickinson), 662
- Secretions, cervical and vaginal, association between biologic action of, on spermatozoa (Laffont and Bourgairel), 920 (Abst.)
effect of, on vitality of spermatozoa (Watson), 920 (Abst.)
- Sex and life (Steinach), 1072 (B. Rev.)
hormones, absence of acute effects of (Dick and Hooker), 1080 (Abst.)
in marriage (Groves and Groves), 1072 (B. Rev.)

Vaginal hysterectomy—Cont'd
 reflections on (Chavannaz), 534
 (Abst.)
 mycosis, vulval and, and trichomoniasis
 (Hesseltine), 641
 Velamentous insertion of umbilical cord
 (Records), 504
 Venous pattern, superficial, in pregnant
 and nonpregnant women by in-
 frared photography, study of
 (Gorman and Hirsheimer), 354
 (Abst.)
 Virilizing disease of women, differential
 diagnostic problem in (West-
 man), 1077 (Abst.)
 Vitamin A content in diets of pregnant
 women (Williams, Hark, and
 Fralin), 1
 in pregnancy (Hirst and Shoemaker),
 12
 and C, activity of, estradiol benzoate,
 and diethylstilbestrol in experi-
 mental fibromatosis (Moricaud
 and Simard), 1081 (Abst.)
 B₁, relation of, to reproductive cycle
 (Williams, Griffith, and Fralin),
 181

Vitamin—Cont'd
 C, concentration of, in blood during and
 after pregnancy (Sadovsky et
 al.), 357 (Abst.)
 K, effect of, administered to patients in
 labor (Fitzgerald and Webster),
 413
 in obstetrics (Hellman, Shettles, and
 Eastman), 844
 Vomiting and nausea of pregnancy due to
 allergic reaction (Finch), 1029
 Vulva, cancer of (Taussig), 764
 Vulval and vaginal mycosis and tricho-
 moniasis (Hesseltine), 641
 Vulvovaginitis, infant, treatment of, with
 estrogenic hormone (Weed and
 Collins), 1082 (Abst.)

W

Washington Gynecological Society, officers
 of, 180, 726

Y

Youth looks at cancer, 1075 (B. Rev.)

Transfusion, renal insufficiency following, of compatible blood (Brainard), 142

Trichomonas vaginalis, pure culture of, pathogenicity and physiology of (Trussell and Plass), 883

Trichomoniasis and vulval and vaginal mycosis (Hesseltine), 641

Triplets, viable, delivered by cesarean section (Smith and Cathcart), 515

Tubal patency, 1920-1940, uterotubal insufflation as test for (Rubin), 628

 pregnancies, successive, coexistent (Behney and Hanes), 155

 pregnancy associated with tubal tuberculosis (Bland), 271

 bilateral simultaneous (Lee and Stone), 316

 sterility, treatment of, total linear salpingostomy for (Challer), 921 (Abst.)

 tuberculosis, tubal pregnancy associated with (Bland), 271

Tuberculin test in pregnancy, significance of (Maeder and Myers), 218

Tuberculosis of cervix (Lahmann and Schwartz), 439

 of endometrium, coincidence of, with tuberculosis of lung (Lackner, Schiller, and Tulskey), 429

 of lung, coincidence of tuberculosis of endometrium with (Lackner, Schiller, and Tulskey), 429

 pelvic (Lahmann and Schwartz), 439

 tubal, tubal pregnancy associated with (Bland), 271

Tubes, permeability of, in adnexal inflammation, research on (Daniel, Mavrodin, and Waneff), 918 (Abst.)

Tuboovarian abscess, pregnancy complicated by (Brougher), 1053

Tumor, Brenner, of ovary complicating labor (Siegel), 337

 granulosa cell, extraovarian (Powell and Black), 318

 intraligamentous (Ragins and Frankel), 302

 of ovary with hemoperitoneum and hemothorax (Vogt), 285

 with precocious sexual development in child aged six (Stabler and Thomson), 1077 (Abst.)

 renal, and ectopic kidney associating or simulating uterine and adnexal tumor (Rubin), 536 (Abst.)

Tumors of internal genitalia among prepubertal girls (Delannoy and Demarez), 139 (Abst.)

 ovarian, changing conceptions of (Taylor, Jr.), 566

U

Umbilical cord, prolapse of (Mengert and Longwell), 79

 velamentous insertion of (Records), 504

Unmarried mother as medical and social problem (Danforth), 637

Urinary incontinence, stress of, method for evaluating (Barnes), 381

 prolan excretion during menstrual cycle (Bagby), 1079 (Abst.)

 tract, infections of, during puerperium, employment of p-aminobenzolsulfonamid in (Brandstrup and Sindbjerg-Hansen), 301 (Abst.)

Urine, ascorbic acid in, relation between elimination of, and interruption of pregnancy (Grossi), 357 (Abst.)

Uterine bleeding, functional, clinical correlates of (Hamblen), 1076 (Abst.)

Uterine bleeding, functional—Cont'd

 testosterone propionate in, and dysmenorrhea (Rubinstein), 1086 (Abst.)

 in last trimester of pregnancy (Wallace), 128

 induced by progesterone (Zondek, Rozin, and Vesell), 391

cancer, treatment of, evaluation of (Healy), 578

cervix, fibromyoma, pedunculated and expelled from vagina, (Torpin and Beard), 490

fibroids need not be operated upon routinely (Vanverts), 173 (Abst.)

 new treatment of (Langlois), 172 (Abst.)

fibroma, hysterectomy for, high partial (Azevedo and Dutra), 173 (Abst.)

hyperkinesia, hormonal treatment of, with corpus luteum hormone (Vautrin), 1084 (Abst.)

motility, mechanical ink writing recorder suitable for recording, during pregnancy and labor (Fenning), 330

retrodisplacement, operation for, and prolapse by reduction and attachment of round ligaments (Taylor), 1026

Uterotubal insufflation as test for tubal patency, 1920-1940 (Rubin), 628

Uterus, adenocarcinoma, mixed, and squamous cell carcinoma of (Skinner and McDonald), 258

 carcinoma of body of (Miller), 791

 carcinosarcoma of (Hoffman), 289

 chorionepithelioma of (Smiley and Clements), 471

 duplex, homolateral hematometra and hematosalpinx in (Arenas and Echegaray), 147 (Abst.)

 fibroids of (Kanter and Klawans), 172 (Abst.)

 fibromyoma angiomasum (Gardner), 822

 gravid, acute torsion of (Olivella and Feo), 1036 (Abst.)

 physics of (Valentinuzzi), 358 (Abst.)

 inversion of, acute, post partum associated with placenta accreta (Halpert and Graffagnino), 509

 lipoma of (Ritter and Stringer), 501

 retrodisplacement of, in relation to pregnancy (Aldridge), 361

 unicornis, right, associated with renal agenesis (Schattenberg and Ziskind), 293

V

Vagina, adenocarcinoma of, primary diffuse (Piper), 498

 artificial, simple method of making (Falls), 906

 congenital atresia of upper two-thirds of, and cervical os with hematometra (Flemming and Kava), 296

 myoma of (DaCosta), 172 (Abst.)

Vaginal bleeding with prolapse and torsion of right Fallopian tube, following vaginal hysterectomy (Bower and Pearce), 1047

 epithelium, glycogen content of, in children (Herrnberger and Horstmann), 110 (Abst.)

 influence of estrin on, of young girls (Herrnberger), 1081 (Abst.)

 hysterectomy (Faure), 534 (Abst.)

 prolapse and torsion of right Fallopian tube with vaginal bleeding following (Bower and Pearce), 1047



The fetal heart sounds were not of the ticktack type in 49 of the cases, the diastole being of greater duration than systole.

The length of ventricular systole ranged from 0.16 to 0.23 second and the diastolic phase from 0.17 to 0.53 second, and there was no constant change in the duration ratio between these periods at the various heart rates.

The heart rates varied from 92 to 163, and, since in all cases, except one with a congenital heart lesion, a healthy child was born, it seems rate changes in this range are of little diagnostic significance.

The first sound is seldom the accented one, this being true in only 8 cases. The intensity of the sounds was about equal in 16 cases and in 28 cases it was greater in the second.

The reported recording of a fetal heart murmur is thought to be the first described in the medical literature.

Congenital heart lesions may be recorded and diagnosed before birth.

A portable mechanism for recording and reproducing fetal heart sounds as well as making them audible directly from the patient is described and it is thought this will be of value (1) clinically, (2) in research, (3) in teaching, and (4) in increasing knowledge of changes, normal or pathologic, of rate and rhythm of the fetal heart sounds during delivery.

REFERENCES

- (1) *Plass, E. P.*: Personal communication. (2) *Strassman and Mussey*: AM. J. OBST. & GYNEC. 36: 986, 1938. (3) *Strassman, E. O.*: Proc. Staff Meet. Mayo Clinic 11: 778, 1936. (4) *Idem*: Ibid. 13: 251, 1938. (5) *Lian, Golblin, and Minot*: Bull. Soc. d'obst. et gynec. 27: 423, 1938. (6) *Pommerenke and Bishop*: AM. J. OBST. & GYNEC. 35: 851, 1938. (7) *Mathews, H. B.*: Ibid. 34: 898, 1937. (8) *DeCosta, E. J.*: J. A. M. A. 111: 2008, 1938. (9) *Orias and Braun-Menendez*: The Heart Sounds in Normal and Pathological Conditions, 1939, Oxford University Press, p. 135. (10) *Hofbauer and Weiss*: Zentralbl. f. Gynäk. 22: 429, 1908. (11) *Beruti, J. A.*: Rev. españ. obst. y ginec. 8: 516, 1923. (12) *Bierring, Bone, and Lockhart*: J. A. M. A. 104: 628, 1935. (13) *Cassio and Fongi*: Am. Heart J. 11: 723, 1936. (14) *Braun-Menendez and Orias*: Presse méd. 44: 603, 1936. (15) *Lewis and Dock*: J. A. M. A. 110: 271, 1938. (16) *Dock, W.*: Arch. Int. Med. 51: 737, 1933. (17) *Eckstein, R. W.*: Am. J. Physiol. 118: 359, 1937. (18) *Wolferth, C. C.*: J. A. M. A. 110: 274, 1938. (19) *Williams and Dodge*: Arch. Int. Med. 38: 685, 1926. (20) *White, P. D.*: Heart Disease, New York, 1931, The Macmillan Co., p. 91. (21) *Boone, B. R.*: Personal Communication and Exhibit A. M. A. Meeting, St. Louis, June, 1939.

1001 FEDERAL SECURITIES BUILDING.

Herrnberger and Horstmann: Glycogen Content of Vaginal Epithelium in Children, Arch. f. Gynäk. 168: 451, 1939.

The smallest amount of follicular hormone which will definitely cause a full and complete glycogen content in the vaginal mucosa in children and maintain it at this level was found to be a daily peroral dose of one thousand international units of estradiol benzoate. The authors' studies show that glycogen accumulation in the mucosa does not occur until after the epithelium has been stimulated by hormone therapy to the point where it has achieved its normal adult type of stratification. They believe that they have proved that the production of normal glycogen content is directly dependent upon ovarian function and that the follicular hormone is directly in control of glycogen formation.

RALPH A. REIS.

The heart was about normal in size but the aorta was wider than normal. A systolic murmur, best heard over the upper sternum and the pulmonic area, was present and was transmitted about equally in all directions.

In the stethogram (Fig. 8), taken over the pulmonic area and part of the upper sternum, normal first and second sounds and a protodiastolic third sound are recorded, while a systolic murmur continuing throughout systole is seen. Systole is longer than diastole.

The electrocardiogram is normal except for a deep Q-wave in Leads II and III and a high T-wave in Leads I and II. In the disc recordings the systolic murmur, taken from over the pulmonic and upper sternal areas, is clearly audible, the rhythm is sinus in origin though variable, and the rate averages 150. No definite diagnosis was made at this time.

VALUE OF RECORDING AND REPRODUCING FETAL HEART SOUNDS

Many accurate, measurable observations are necessary to overcome misinformation concerning the normal fetal heart, and it is believed the methods described can be the principal means of doing this.

For teaching purposes a collection of records showing normal and abnormal fetal heart sounds can be made and reproduced so students can unquestionably see and hear what is being described.

Records can be taken during the course of pathologic cases, ablatio placentae, for example, and preserved to actually show the progression of the disease from the fetal heart standpoint.

The records will be of permanent value in studying the fetal heart response to drugs administered to the pregnant mother before and during confinement.

The records can be reproduced at leisure and the heart studied as many times as desired without alarming or tiring the patient.

Fetal heart sounds are an unsolved mystery as far as the average medical student is concerned, and some practitioners as well, but after he actually sees and hears the recorded sounds and hears those audited directly from the patient until he is familiar with their vagaries he is then prepared to auscultate the organ from which they emanate.

By broadcasting the heart sounds through the loud speaker, all in the delivery room can follow the normal changes in the fetal sounds, and to those of us who have done this, it is evident much time and study will be necessary before the normal and pathologic fetal heart changes can be differentiated.

When it is necessary to decide whether the child is alive or not this adds another method of examination and, with electrocardiography, it would be a rare case in which this question could not be accurately answered.

It is believed that, by this method, congenital heart lesions can usually be discovered before birth.

SUMMARY

In a series of 58 pregnant mothers, an attempt was made to make stethograms and reproducible disc recordings of the fetal heart. In 52 cases the effort was successful and in 6, unsuccessful.

The age of the fetuses whose heart sounds were recorded varied from five and one-half months to the time of delivery.

TABLE I. DATA ON LOCHIA

DAYS POST PARTUM	SERIES A (CASES GIVEN ERGOTRATE)					SERIES B (CONTROLS)				
	PER CENT OF PATIENTS WITH					PER CENT OF PATIENTS WITH				
	PROFUSE LOCHIA	MODERATE LOCHIA	SCANT LOCHIA	NO LOCHIA	LOCHIA ALBA	PROFUSE LOCHIA	MODERATE LOCHIA	SCANT LOCHIA	NO LOCHIA	LOCHIA ALBA
1	0	62	36	0	0	0	73	27	0	0
2	1	44	54	0	0	1	61	38	0	0
3	0	39	59	0	1	2	63	34	0	0
4	0	37	63	0	3	0	68	32	0	1
5	0	40	59	0	4	2	63	35	0	1
6	0	28	52	9	6	1	46	52	1	0
7	0	22	66	10	20	1	43	55	0	1
8	1	23	68	9	23	0	45	55	1	11
9	0	23	45	11	33	0	40	56	6	19
10	0	31	57	9	33	0	49	43	8	43

TABLE II

<i>Series A (Patients given ergotrate):</i>		
Primiparas		72
Multiparas		28
Total		100
Primiparas having afterpains		40 (55%)
Multiparas having afterpains		25 (89%)
Total		65 (65%)
<i>Series B (Controls):</i>		
Primiparas		91
Multiparas		9
Total		100
Primiparas having afterpains		39 (42%)
Multiparas having afterpains		8 (88%)
Total		47 (47%)

The standard of morbidity used was an elevation of temperature to 38° C. or over for two or more consecutive days. Temperature elevations due to causes other than uterine infection were not included in the morbidity statistics.

RESULTS

The determination of the rate of involution of the uterus was made by plotting graphically the mean average height of the fundi each day in each group of cases considered. Fig. 1 shows the rate and degree of involution of the 100 cases (Series A) receiving ergotrate during the first three post-partum days as compared to the same number of controls (Series B). Although the mean difference in the measurements amounts to about 0.5 cm. only, it is significant that the mean height of the fundi in Series A is at all times less than that of Series B. It is also significant that the rate of involution in Series A is a regular one throughout the period while that of Series B tends to slow down particularly in the last three days of the ten-day period.

Believing, as many have observed in their clinical experience, that multiparas involute less rapidly than primiparas, I compared the cases graphically in the group receiving ergotrate and the controls. Fig. 2 illustrates the comparative involution in multiparas and primiparas who received ergotrate. Surprisingly enough, the rate of involution in multiparas on ergotrate prophylaxis follows very closely that of primiparas. In Fig. 3, however, where the multiparas and primiparas of the control series are compared, it is seen that the involution of the multiparous uterus

THE REDUCTION OF POST-PARTUM MORBIDITY BY THE PROPHYLACTIC USE OF ERGONOVINE*

JAMES B. LOUNSBURY, M.D., ANN ARBOR, MICH.

THE employment of an oxytocic immediately post partum has been practiced ubiquitously since John Stearns introduced the use of ergot in obstetrics in 1807. Few obstetricians, however, are convinced that the routine administration of such a drug over a period of several days is warranted.

Since the appearance of the article by Bourne and Burn¹ in 1927, a number of clinical experiments²⁻⁶ have been made in an effort to demonstrate the prophylactic value of ergot and its derivatives. With the controversial⁷⁻¹⁰ isolation of the active principle of ergot, now known under the pharmacopeial name of ergonovine,¹¹ an added interest in the subject was aroused. The time-honored fluid extract of ergot is now being abandoned to the more stable active principle.

The inconsistency in the results reported with the prophylactic use of the fluid extract of ergot has been enlightened by the work of Jones and Barlow⁵ showing that the drug may undergo deterioration. Since the advent of ergonovine, studies on its effect on involution and puerperal morbidity have been invariably favorable.¹²⁻¹⁶ The following study, undertaken at the Maternity Division of the University Hospitals in Cleveland, will add to the literature which has been accumulating since 1935.

PROCEDURE

Two hundred obstetric patients were studied (Table II), unselected except as follows: Patients with abdominal tumors, patients on whom observations were too inadequate to be of use, cesarean sections and very ill patients, such as cardiacs, were discarded for obvious reasons. Due to the nature of the University Hospitals' obstetric service, nearly all the cases were operative deliveries, the term operative including the so-called outlet or prophylactic forceps.

All patients received the routine administration of 1 c.c. of pituitrin (obstetric) following delivery of the fetus and 0.2 mg. of ergotrate (Lilly) following delivery of the placenta, both drugs given hypodermically. The first 100 cases, Series A, were given in addition 0.4 mg. of ergotrate orally six hours post partum and 0.2 mg. t.i.d. for the next three post-partum days. The second 100 cases, Series B, were given no oxytocic other than the routine pituitrin and ergotrate immediately post partum as noted above, unless alarming subinvolution, post-partum hemorrhage or foul lochia warranted further medication.

Daily measurement of the height of the fundus above the symphysis pubis, notation of the character and amount of lochia, and interrogation of the patients as to the presence and severity of afterpains were made by the same individual. Measurements were discarded when it was known or suspected that the urinary bladder was full. Uterine pains known to be associated with the process of nursing were not tabulated.

*The clinical work of this article was done while the author was a member of the resident staff of the Maternity Division, University Hospitals, Cleveland.

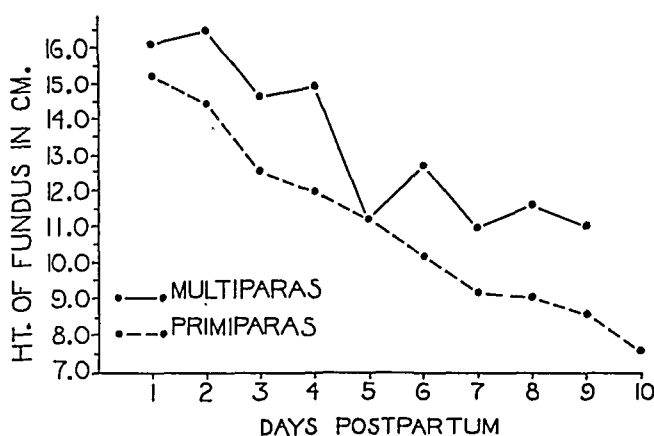


Fig. 3.—The involution of the multiparous uterus (solid line) compared to that of the primiparous uterus (broken line), neither of which groups was given the prophylactic course of ergotrate.

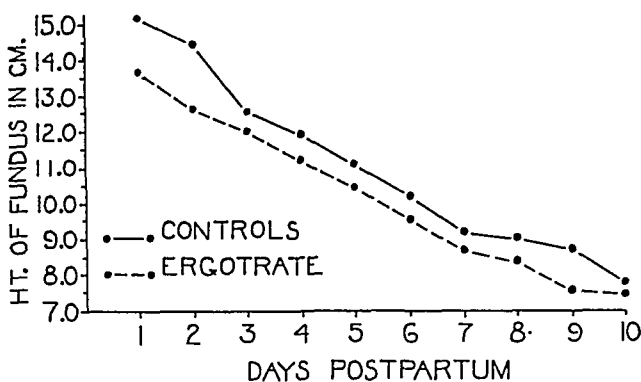


Fig. 4.—The rate and degree of involution of the uteri of the primiparas who were given ergotrate (broken line) and of those who were not (solid line). The mean difference of the two curves is about 0.5 cm.

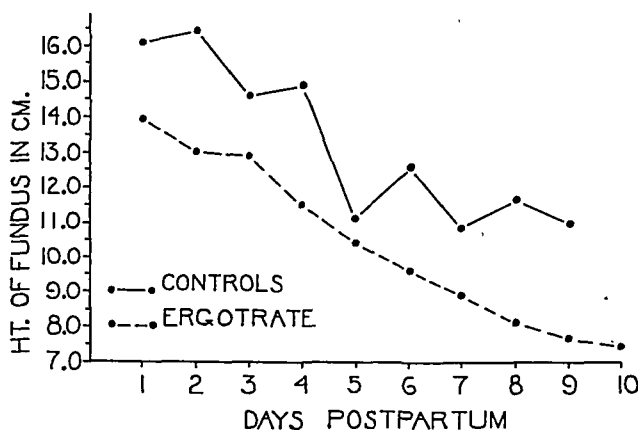


Fig. 5.—This graph illustrates the rate and degree of involution of the uteri of multiparas who received ergotrate (broken line) and those who followed the customary course without prophylactic medication (solid line). The mean difference of these two curves is 1.5 cm.

is considerably more irregular and more delayed than the primiparous uterus with or without the administration of ergotrate.

In the use of prophylactic therapy with ergotrate, the effect on primiparas alone is shown in Fig. 4. Here again the actual difference in the mean height of the fundi does not amount to more than 0.5 cm., but it can be seen that there is a definite trend or tendency for the rate and degree of involution in the cases receiving ergotrate to be somewhat better than the controls. The same type of comparison is made in Fig. 5 with respect to the effect of ergotrate on the multiparous uterus, as compared to the rate of involution in the control. Here the benefit derived from oxytocic administration is much more marked, the measurements of the fundi averaging almost 1.5 cm. in difference.

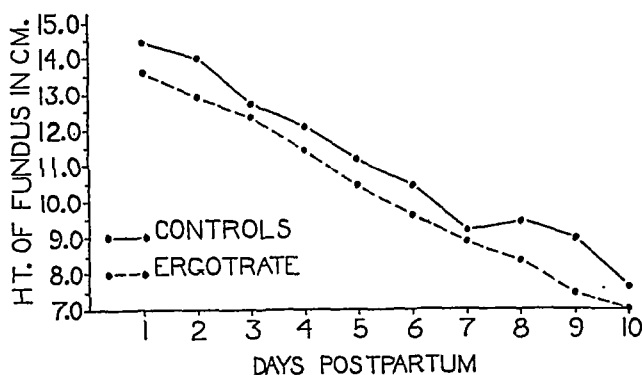


Fig. 1.—Graph showing the rate and degree of involution of the uterus of patients given ergotrate (broken line) during the first three post-partum days compared to the controls (solid line) who received only the routine oxytocics during delivery. The average height of the fundi in each group is plotted for each day of the post-partum period in the hospital. Notice the regularity of the line representing the uteri influenced by ergotrate and the irregularity of the controls; the latter show a tendency for the rate to decrease during the last three days.

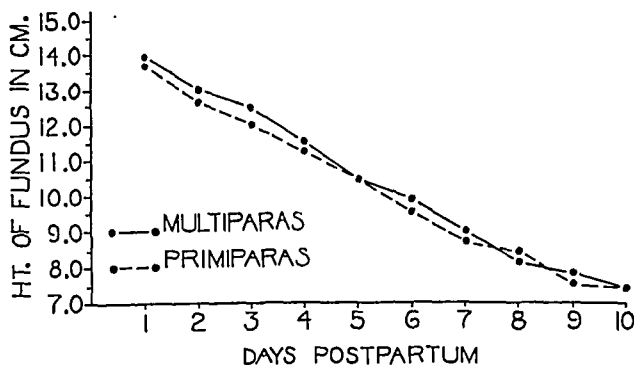


Fig. 2.—The curves, plotted in the same manner as in Fig. 1, show how closely the involution of the multiparous uterus (solid line) follows that of the primiparous uterus (broken line) when ergotrate is given during the first three days of the post-partum period.

A statistical study of the puerperal lochia can at best be rather inaccurate due to the inherent difficulty in determining the exact amount of lochia passed and due to the indefinite borderlines defining lochia rubra, lochia serosa, and lochia alba. In this study it is admittedly quite inaccurate in view of the fact that the description of the character and amount of lochia was based purely on personal judgment or impression. Since it may be assumed, however, that the same relative inaccuracy pertains to Series A as to Series B of the patients or, in other words, that the same percentage of error applies to the one group as to the other, some conclusion perhaps may be justified from a study of Table I. The cases are

in showing that the patients who were given ergotrate had a better and smoother post-partum course from the standpoint of clinical signs during the post-partum period.

The studies show that there is definitely a more regular rate of involution in the patients who received prophylactic doses of ergotrate than in those who were allowed to follow their own course. The work of Davis and his co-workers⁷ on uterine tone and motility showed that some primiparas and most multiparas tend to exhibit irregularities. It is at the time of these irregularities which are unpredictable that the complications of involution may develop, chiefly post-partum hemorrhage and retention of lochia favoring puerperal sepsis. It seems reasonable to assume that if these irregularities can be prevented by the routine administration of a nontoxic drug such as ergonovine, the complications which may arise from the irregularities of tone and motility will be prevented. It may be that it would be advantageous to administer the drug over a longer period of time during the puerperium, not with the idea of hastening involution, but with the intention of keeping the involution of the uterus at a regular rate of progression until the uterus has returned to normal size. A case in point is that of a para iii who developed post-partum hemorrhage from subinvolution on the twenty-first day of the puerperium. It may be conjectured that if she had been receiving an oxytocic up to this time the emergency would not have developed. Further work on the toxicity of ergonovine over prolonged periods of administration must be done before such therapy can be advised.

I would like to propose the hypothesis that many uteri do not have the ability to maintain adequate tonic contraction for one reason or another; that there is thus a lag in the effectiveness of the contractions, a lag behind the rate that the organ is undergoing atrophy. Following evacuation of the placenta many injured blood sinusoids are left exposed on the inner wall of the uterus. Experience has shown how brisk the bleeding from these vessels may become. Compression of a bleeding blood vessel is a fundamental surgical principle in the control of hemorrhage. Compression of these exposed vessels is accomplished more or less by the rhythmic motility and contraction of the uterus which continues after delivery. But while the uterus is carrying on its rhythmic contraction, it is also undergoing a tremendously rapid atrophy. The atrophy is a process of catabolism of the individual cells of the myometrium whereby the cells become smaller in all dimensions, but chiefly in breadth. The contraction of the uterus, however, is due to a shortening of the fibromuscular cells in their longitudinal diameter. It is this shortening which exerts the effective pressure on the open sinusoids and prevents bleeding until the vessels have firmly thrombosed. If the contraction of the cells of the myometrium is not frequent and persistent enough to take up the slack produced by the process of atrophy, a relative flaccidity of the uterus is allowed to develop. Thus the effect of compression of the bleeding blood vessels is lost. The process may vary in degree so that the bleeding which is allowed to occur may be only the oozing which forms "lochia" or may be actual hemorrhage. It may be

classified on each day of the ten-day post-partum period according to the amount of lochia passed. The greatest difference to be noticed in the two groups is in the incidence of lochia observed to be profuse and in the cases showing absence of lochia. Whereas only 2 per cent of those receiving ergotrate exhibited profuse lochial discharge, there was 7 per cent in the control group; and while the absence of lochia was found in 48 per cent of patients in Series A, it was observed in only 16 per cent of the controls. Likewise, Table I demonstrates the greater prevalence of the appearance of lochia alba in the group receiving ergotrate than in the controls.

A study of the incidence of "afterpains" in the primiparas and the multiparas of the two groups reveals some rather interesting facts (Table II). Of the 100 cases in Series A, 65 per cent had afterpains, while 47 per cent of the controls suffered afterpains. In Series A, 55 per cent of the primiparas had pains, while 42 per cent of those who received no ergotrate had afterpains. In the cases given ergotrate 89 per cent of the multiparas had afterpains, while 88 per cent of the multiparas in Series B had afterpains. It is seen, therefore, that the incidence of afterpains in the multiparas in the two groups was practically identical, while the incidence in the primiparas was only a little greater in those who were given ergotrate than in the controls. Incidentally, the occurrence of afterpains in primiparas does not seem to be so infrequent as is commonly believed.

The puerperal morbidity as determined by the standard mentioned above, that is, the morbidity due to uterine infection excluding all other causes, was found to be 4 per cent in the cases given ergotrate as compared to 10 per cent in the controls.

Side reactions of ergot therapy such as nausea and vomiting which occur with the fluid extract were not seen. There was no case of ergotism.

COMMENTS

The size of the dosage of ergotrate and its frequency of administration were chosen purely arbitrarily. It was felt that if 0.2 mg. of the drug would stimulate the tone and motility of the uterus, as shown by Davis and others,⁷ for a period of at least two or three hours, little would be gained by subjecting the patient to the possible pain of more vigorous contractions. As shown in this series, the presence of afterpains was relatively little increased by the use of the drug in this dosage. Afterpains were readily controlled by codeine. It may be that the use of greater or more frequent doses of ergonovine would produce an even more marked exhibition of the value of the prophylactic administration of an oxytocic.

The impression was gained that the toxemias tended to involute much more rapidly than the normal cases. An attempt was made to compare the rates of involution of toxemias to normal cases in the group receiving ergotrate and in the control series by the same graphic method already presented. The group of cases of toxemias was too small, however, to be statistically utilizable and the results were too irregular to be of significance. The impression is maintained, none the less, that toxemias, especially eclamptics, tend to involute much more rapidly than normal puerperal cases.

The lack of accuracy obtainable in a study of this sort may make one discredit the results. It must be observed, however, that whatever inaccuracies in measurements and in observations occurred in the group of patients who were given ergotrate occurred to a like extent in the controls. More significant, however, in justifying the conclusions drawn is the fact that there is consistency in all the subdivisions of the study

A STUDY OF 1,200 CASES OF HYSTERECTOMY*

PHILIP H. SMITH, M.D., F.A.C.S., EVANSTON, ILL.

(From the Department of Obstetrics and Gynecology, Evanston Hospital and the Northwestern University Medical School)

REMOVAL of the uterus constitutes a large percentage of the surgery in the Department of Obstetrics and Gynecology at the Evanston Hospital. The operation is done for varied findings and many symptoms. Since several types of procedure are employed, we have felt that a study of our work would be of general interest and should enable us better to evaluate our results.

During the period October, 1929, to Jan. 1, 1940, we have done 1,200 hysterectomies. Of these, 744 were subtotal, 93 were total abdominal, and 363 were vaginal operations.

It is of interest that of the 363 vaginal hysterectomies, 275 have been done in the last five years, and that none were done the first year included in the study (1930). The peak of this incidence was the year 1937. Added experience, improvement in technique and the encouraging results reported from other clinics influenced us in our frequent selection of the vaginal route. It is impossible to have hard and fast rules governing the choice of operation, but excluding cases of known uterine cancer, residues of pelvic infection, adnexal pathology which must be dealt with otherwise, extremely large tumors and postoperative adhesions, our choice is usually the vaginal operation.

This operation is especially adapted to women in whom there is some relaxation of the pelvic floor and supporting structures, and in the presence of cervical disease and retrodisplacement. It lends itself to the repair of this relaxation by doing either anterior or posterior colporrhaphy, or both, and, of course, does away with the cervix. In the presence of complete prolapse and in those patients in whom the uterus protrudes only partially from the introitus, the interposition of the broad ligaments beneath the bladder, following the removal of the uterus through the vagina, has given us satisfactory results in most cases.

In some clinics the Manchester operation is preferred. One member of our group is using it now more often than formerly. It may well be that we have not accorded it the place it deserves. This, however, is a report on hysterectomy and is intended to show what we have been able to accomplish with that operation.

We regularly employ the total abdominal operation in known cases of carcinoma of the corpus. We have no knowledge of carcinoma appearing in the cervical stump in any of the 744 cases of subtotal hysterectomy included in this report. More important, however, is the fact that the pathologist discovered early cancer of the uterus in 18 patients

*Presented before the Chicago Gynecological Society, March 15, 1940.

inferred that the effect attempted in the use of an oxytocic is to assist this deficiency in tone and to maintain a rhythmic contraction of the uterus sufficient to keep pace with the atrophy of the organ.

CONCLUSIONS

1. The prophylactic administration of ergonovine in the form of ergotrate (Lilly) over several days in the post-partum period:

- a. Increases the rate of involution of the uterus;
- b. Produces a more regular rate of involution with fewer periods of greater or lesser subinvolution;
- c. Results in a decrease in the amount of and the sanguineous nature of the lochia;
- d. Reduces the puerperal morbidity due to uterine infection.

2. The rate and extent of involution in multiparas closely approximates that of primiparas when ergonovine is administered during the first three days of the puerperium.

3. The use of ergonovine in the post-partum period as prophylaxis is particularly beneficial in multiparas.

4. Normally multiparas have a less rapid and less regular rate of involution than primiparas.

5. Afterpains are, contrary to the usual belief, quite common in primiparas.

6. Ergotrate, in the dosage used in this study, increases only slightly the incidence of afterpains.

7. The prophylactic use of an oxytocic in the post-partum period is based on the fundamental surgical principle of hemostasis by compression.

SUMMARY

1. The effect of the routine administration of ergonovine during the first three days of the post-partum period was studied in 200 obstetric patients, primiparas and multiparas. One hundred patients were given the drug and 100 patients were used as controls.

2. The prophylactic use of ergonovine in the puerperium resulted in an increase in the rate and extent of involution, in a decrease in the amount and sanguineous character of the lochia, and in a decrease in puerperal morbidity due to uterine infection.

REFERENCES

- (1) Bourne, A., and Burn, J. H.: J. Obst. & Gynaec. Brit. Emp. 34: 249, 1927.
- (2) Greenhill, J. P.: New England J. Med. 205: 274, 1931. (3) Sühs, J.: M. J. & Rec. 136: 468, 1932. (4) Der Brucke, M. G.: AM. J. OBST. & GYNEC. 29: 272, 1935. (5) Jones, J. L., and Barlow, O. W.: Ibid. 29: 489, 1935. (6) Livingston, F. H., and Blum, S. G.: Am. J. Surg. 31: N. S.: 533, 1936. (7) Davis, M. E., Adair, F. L., Rogers, G., Kharasch, M. S., and Legault, R. R.: AM. J. OBST. & GYNEC. 29: 155, 1935. (8) Dudley, H. W., and Moir, Chassar: Brit. M. J. 1: 520, 1935. (9) Stoll, A., and Burchhardt, E.: Bull. d. sc. pharmacol. 42: 257, 1935. (10) Thompson, M. R.: J. Am. Pharm. A. 24: 748, 1935. (11) Report of Council on Pharmacy and Chemistry, J. A. M. A. 106: 1008, 1936. (12) Erichsen, F.: Zentralbl. f. Gynäk. 62: 788, 1938. (13) Kushner, J. I., and Wahrsinger, P. B.: AM. J. OBST. & GYNEC. 35: 859, 1938. (14) Davis, M. E., Adair, F. L., and Pearl, S.: J. A. M. A. 107: 261, 1936. (15) Beecham, C. T.: AM. J. OBST. & GYNEC. 32: 330, 1936. (16) Tuck, F. L.: Ibid. 30: 718, 1935.

TABLE III. PREVIOUS GYNECOLOGIC OPERATIONS

TYPE OF OPERATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Bilateral oophorectomy	3	2	0
Bilateral salpingectomy	18	1	0
Unilateral oophorectomy	47	5	4
Unilateral salpingectomy	27	1	4
Uterine suspension	46	10	9
Vaginal plastic operations	23	1	17
Exploratory laparotomy	7	0	0
Removal of ovarian cysts	13	4	0
Radium therapy	7	8	0
Ectopic pregnancy	5	2	2
Removal of tumors (myomectomy)	7	4	1
Amputation of cervix	9	4	0
Sterilization operation	4	0	0
Hysterotomy	3	0	0
Drainage of abscess	4	0	0
Repair of vaginal fistula	2	0	1
Resection of ovary	3	0	0
Transposition operation	0	0	2
X-ray therapy	0	5	0
Diagnostic dilatation and curettage	37	12	0

TABLE IV. ADDITIONAL OPERATIVE PROCEDURES

PROCEDURE	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Bilateral oophorectomy	157	39	4
Bilateral salpingectomy	177	39	5
Unilateral oophorectomy	199	11	7
Unilateral salpingectomy	162	9	5
Appendectomy	227	15	1
Anterior colporrhaphy	24	4	114
Posterior colporrhaphy	62	4	256
Diagnostic dilatation and curettage	19	10	12
Ovarian cysts removed	13	0	4
Bartholin cysts removed	0	0	2
Cervical plastic	33	0	0
Resection of ovary	16	0	0
Herniotomy	6	0	0

The bladder was opened three times while operating abdominally and twice while doing vaginal hysterectomy. Careful closure and the use of a retention catheter for some days resulted in satisfactory healing.

The bowel was opened three times while doing difficult dissections in the pelvis and twice while doing posterior colporrhaphy following vaginal removal of the uterus. With the exception of a fistula which remained open for six months in one of the subtotal operations, these patients made good recoveries.

Unless the operation is quite difficult and a stormy convalescence anticipated, or when much time has been consumed, we regularly remove the appendix. Two hundred forty-two appendectomies were done following the subtotal and total hysterectomies. Of the remaining cases many had previously had their appendices removed. Convalescence when appendectomy was done was no more stormy than when the appendix was allowed to remain. The average stay in the hospital was 15.4 days, and the morbidity of this group was 23 per cent.

The ten vaginal wound infections listed in Table V include only those of severe grade in which there was frank suppuration. I am sure that infection of the vaginal wound in a lesser degree accounts for much of the postoperative morbidity in this group.

In the treatment of complications, blood transfusions were given sixty times.

The average number of days spent in the hospital was 15.6. This does not represent the postoperative days. Many patients come in for examination several days before operation and this increases the average length of stay.

in whom the cervix had been allowed to remain. A more routine use of the total procedure would have given these women additional protection. For the period as a whole only one out of nine abdominal operations has included the removal of the cervix. I wish to point out that this ratio is changing rapidly. In 1939, we did exactly twice as many total operations as in 1938.

Of these 1,200 women, 901 were multiparas and 299 were nulliparas. Of the 363 vaginal hysterectomies, 348 were multiparas and 15 were nulliparas.

The chief symptoms complained of in the order of their frequency were: vaginal bleeding, 711 (60 per cent); pain and discomfort, 471 (30 per cent); backache, 243 (20 per cent); leucorrhea, 154 (14 per cent); urinary disturbance, 141 (12 per cent); pressure, 49 (4 per cent). One hundred fifty-four either noticed enlargement or their physician had discovered a tumor. Seventy-seven (6 per cent) complained of a protrusion from the vagina and 34 (3 per cent) complained of a loss of weight.

TABLE I. AGE INCIDENCE

Under 21 years	4
21 to 30 years	57
31 to 40 years	450
41 to 50 years	503
51 to 60 years	113
61 to 70 years	58
Over 70 years	15

Because it is unusual to remove the uterus in a patient under 21 years, I wish to say that two of these girls, aged 17 and 19, had large degenerating fibroid tumors of the uterus. The uterus could not be saved. The remaining two, both aged 19 years, had residues of pelvic infection; their symptoms of pain and bleeding, and the presence of old inflammatory masses, brought them to operation. Both ovaries were preserved in the first two cases, and one ovary each in the other two.

TABLE II. INDICATIONS FOR OPERATION

INDICATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Fibroids	460	48	124
Functional bleeding	84	9	18
Prolapse	0	0	114
Pelvic inflammatory disease	61	9	0
Descensus and relaxation	0	0	67
Retroversion	24	0	32
Carcinoma	23	17	7
Ovarian cysts	25	5	0
Endometriosis	16	2	0
Postoperative adhesions	13	0	0
Tuberculosis (pelvic)	6	0	0
Tuboovarian abscess	6	0	0
Bilateral dermoid cysts	5	0	0
Twisted ovarian cysts	2	0	0
Ectopic pregnancy and fibroids	2	0	0
Pregnancy and multiple fibroids	2	0	0
Brenner tumor of ovary	1	1	0
Uterus perforated with curette	2	0	0
Fibroma of ovary	2	0	0
Sarcoma and sarcomatous degeneration	7	0	0
Bicornate uterus	1	0	0
Squamous cell carcinoma of cervix	1	2	1
Hydatidiform mole	1	0	0

eighteen hours later, and the abdomen found to be full of blood. The patient went into shock. Sutures were inserted around the cervical and broad ligament stumps, and two blood transfusions were given. She developed peritonitis and died on the fourth postoperative day.

CASE 2.—The patient, aged 37 years, was operated upon for fibroid of the uterus, endocervicitis, and perineal relaxation. Perineorrhaphy, cervical plastic and subtotal hysterectomy were done. The patient developed acute rheumatic fever, and died on the nineteenth postoperative day. Post-mortem examination revealed acute ulcerative endocarditis and fibropurulent pericarditis.

CASE 3.—The patient, aged 44 years, was operated upon for residue of pelvic infection. Dissection was difficult. She died on the sixty-ninth postoperative day of progressive infection.

CASE 4.—The patient, aged 42 years, was operated upon for fibroids. She died on the operating table, as the abdomen was being closed, of respiratory failure. All attempts at resuscitation were futile.

CASE 5.—The patient, aged 54 years, was operated upon for fibroids. She developed peritonitis and intestinal obstruction. An enterostomy was done, but the patient died on the twentieth postoperative day.

CASE 6.—The patient, aged 74 years, was operated upon for fibroids and ovarian cysts. She died on the fifth postoperative day of pulmonary embolism.

636 CHURCH STREET

DISCUSSION

DR. IRVING F. STEIN.—That no deaths occurred after either total or vaginal hysterectomy is indeed worthy of note and a 0.5 per cent mortality for the entire series is enviable.

Concerning indications for vaginal hysterectomy, I find complete agreement with our own. I am particularly eager to stress the exclusion of those women who have evidence of pelvic residues and postoperative adhesions.

That no cases of stump carcinoma appeared in a ten-year period out of 744 cases of subtotal hysterectomy is to me quite remarkable. I recently learned that in the Tumor Clinic of Michael Reese Hospital, 9 such cases were discovered in the past two years. In view of this finding, we have seriously considered the advisability of extending our indications for total hysterectomy. At Mayo Clinic, total hysterectomy is done 3.4 times as often as the subtotal. They had 538 total hysterectomies in 1938 with 4 deaths; 156 subtotal, with no deaths; 165 vaginal, with 1 death; and 9 Wertheim with no deaths. In Dr. Smith's series, subtotal was the majority group and in this group only was their mortality.

I should like to ask whether there were no ureteral injuries during or following hysterectomy. In total hysterectomy especially, there is danger of ureteral injury, particularly so in cases of intraligamentary fibroids.

DR. H. O. JONES.—In a recent annual survey made in our hospital, results somewhat similar to those reported by Dr. Smith were obtained. There has been a gradual increase in the number of patients treated by vaginal hysterectomy. In a comparable series of vaginal and complete abdominal hysterectomies, we found a marked difference in favor of the vaginal procedure, morbidity and hospital stay less, fewer complications, reduced discomfort, and no mortality. Measuring the discomfort by sedatives used postoperatively, the vaginal cases required 25 per cent less.

Pulmonary embolism still remains one of our most dreaded complications especially in abdominal surgery. I wish to ask Dr. Smith whether his patients are subjected to any procedures which have, as a purpose, the increase of the circulation, to reduce the likelihood of phlebitis and embolism. Do you make it a point of having your patients out of bed at an early date?

In looking over our patients with phlebitis and embolism, we have not found one after vaginal procedures. A similar observation was made by another member of this Society in a very large consecutive series of vaginal hysterectomies.

TABLE V. POSTOPERATIVE COMPLICATIONS

COMPLICATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Wound infection	12	3	10
Pelvic infection	12	2	4
Bleeding	7	1	7
Hematoma	3	0	2
Peritonitis	8	2	2
Pelvic abscess	4	0	2
Pyelitis	3	1	5
Pneumonia	3	0	1
Pulmonary embolism	4	0	0
Phlebitis	1	0	2
Psychosis	3	0	0
Bowel obstruction	2	1	0
Rectal abscess	2	0	0
Empyema	1	1	0
Rheumatic fever (acute)	1	0	0
Ventral hernia	1	0	0

TABLE VI. MALIGNANCIES

Fundus:	33 adenocarcinomas
	2 papillary adenocarcinomas
	1 squamous cell carcinoma
	5 sarcomas
	2 sarcomatous degeneration of fibroids
	1 polypoid adenocarcinoma
	1 chorionepithelioma
Ovary:	4 adenocarcinomas
	1 malignant parvilocular ovarian adenoma
	2 papillary adenocarcinomas
Cervix:	2 adenocarcinomas
	3 squamous cell carcinomas
Tube:	1 papillary adenocarcinoma

The morbidity for all cases, using the American College of Surgeons standard, i.e., a rise to 100.4° F. on any two days excluding the day of operation, is 34 per cent. For the subtotal group it is 28 per cent; for the total, 46 per cent; and for the vaginal, 42 per cent.

Twenty-one patients returned to us because of gynecologic complications. Twelve returned, following subtotal hysterectomy, 3 because of bleeding from the cervical stump. In these cases, the cervix was removed. Three more were operated upon for ovarian cysts, and 3 for genital prolapse. A Sturmdorf operation was done on another because of cervical disease. Two women returned in whom cancer was found. One was found to have cancer of the ovary, and the other, cancer of the retroperitoneal lymph glands.

Six patients have returned following vaginal hysterectomy, 3 because of late pelvic abscesses, which were drained, and 2 because of recurrent rectocele and cystocele. On one of them a modified Le Fort operation was done and on the other an anterior and posterior colporrhaphy.

Three patients who had been subjected to complete hysterectomy for corpus cancer returned with large pelvic masses. In 2 of these cases, the abdomen was opened again, but advanced carcinomatosis precluded further surgery.

In the complete series there were 6 deaths, giving a mortality rate of 0.50 per cent. As none of these deaths were in the total or vaginal hysterectomy groups, the mortality rate for those groups was zero. Thus the mortality rate for the subtotal group, in which all the deaths occurred, is brought up to 0.80 per cent.

A brief discussion of each fatal case follows:

CASE 1.—The patient, aged 33 years, was operated upon for myopathic bleeding and retroversion. There was postoperative bleeding. The wound was opened

and panhysterectomy with or without salpingo-oophorectomy. Although in such a series there were a number of preoperative handicaps, such as diabetes, hypertension, secondary anemia, etc., these have been disregarded in the interest of simplicity, and the recorded postoperative morbidity and mortality given without reference to pre-existing hazards.

The main object of this analysis was the determination of the postoperative morbidity and mortality, interest centering in a comparison between those of supravaginal hysterectomy and panhysterectomy. But several other subjects claimed sufficient attention to be included in the discussion. Many of these details, as discussed in the next paragraph, are embodied in Table I.

TABLE I. DETERMINATION OF POSTOPERATIVE MORBIDITY AND MORTALITY

NO. OF CASES	TYPE OF OPERATION	AVERAGE AGE	COLOR		SEDIMENTATION TIME IN MINUTES	OPERATING TIME	APPENDECTOMIES	AVERAGE DAY OF DISCHARGE
			WHITE	COLOR				
79	Simple supravaginal hysterectomy	37	47	32	86	83	41	17
46	Supravaginal hysterectomy without pelvic inflammatory disease	40	30	16	72	74	11	17
96	Supravaginal hysterectomy with pelvic inflammatory disease	35	72	24	68	78	30	18
35	Supravaginal hysterectomy with minor operations	38	24	11	119	108	12	16
44	Panhysterectomy	50	40	4	122	96	3	18

ANALYSIS OF CASES

There were 79 cases of simple supravaginal hysterectomy, the ages of the patients ranging from 25 to 55 years. In this group 47 patients were white and 32 colored. The average sedimentation time was 86 minutes. In 41 cases appendectomy was done. The average operating time was eighty-three minutes—five to ten minutes longer than in the groups in which salpingo-oophorectomies were included but the appendix less frequently removed.

The group of supravaginal hysterectomy with salpingo-oophorectomy without pelvic inflammatory disease totaled 46 cases, 30 white and 16 colored, with an average age of 40 years. The average sedimentation time here was 72 minutes. Only 11 appendectomies were done and the average operative time was 74 minutes. The group of supravaginal hysterectomy with salpingo-oophorectomy, because of the presence of pelvic inflammatory disease, was the largest of all, numbering 96. This is probably explained by the fact that both hospitals concerned draw a large part of their ward patients from negro sections of the city. In the given group, 72 were colored patients and 24 white. The average age was the lowest of the five groups, being 35 years. The sedimentation time also was lowest, averaging 68 minutes. Operative time averaged 78 minutes, with 30 associated appendectomies. The smallest group comprised supravaginal hysterectomy in addition to minor operations. There were 35 of these with 12 appendectomies included. In this group, in contrast with the last, 24 of the patients were white and only 11 were colored. The average age was 38 years. Obviously the longest operating time occurred in this series. It was 108 minutes. Notwithstanding this, the average hospitalization was shortest in this group.

DR. CHARLES E. GALLOWAY.—In the community where we work we do not see any carcinomas of the cervical stump recurring in patients who have had subtotal hysterectomy. That does not mean there are none, but on the other hand we are so situated that we would be very likely to see most of them.

We are not inclined to insert drains in doing a total abdominal hysterectomy. In the series reported we opened the bladder five times and injured the rectum five times, but not with any great harm. Regardless of how much care we take it seems that once in a while we have an accident.

There are many men who think an appendix should be left alone if it is normal. In this country, however, where women as well as men are likely to find themselves in the future in places where medical attention will not be given promptly, we feel that if it is a favorable case and things have gone along all right through the hysterectomy the appendix should be removed.

We do not seem to be able to get rid of the febrile morbidity associated with vaginal hysterectomy. Forty-two per cent of our patients had fever following vaginal hysterectomy for more than two days, some of them fairly high fever. We are now making vaginal cultures of every vaginal hysterectomy that comes to the operating room to see if we can learn anything from such a study.

DR. SMITH (Closing).—We use no retention catheter except occasionally in a case of extreme retention. Neither do we drain in either total or vaginal hysterectomy. We do put a pack in place in the vaginal operation which remains for twenty-four hours. We inject pituitrin into the cervix as we start the vaginal operation.

In answer to Dr. Jones' question about pulmonary embolism, we do nothing to lessen the incidence. I do not know why the incidence is low. We allow our patients out of bed from the eighth to the tenth day, those who have had vaginal hysterectomies about the eighth day and most of those who have had abdominal hysterectomies around the tenth day.

Concerning Dr. Galloway's discussion about morbidity, I was sorry when I completed this study that I had not kept track of the number of days the patient was morbid. In a paper Dr. Richardson presented some years ago he stated that for morbidity to mean anything, one should know how long the patient was morbid. If a patient is morbid for a week or longer, the after-effects of this morbidity are likely to be much different and of greater consequence than of patients who have only two or three days of morbidity.

AN ANALYSIS OF THREE HUNDRED HYSTERECTOMIES

DOROTHY L. ASHTON, A.B., M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Department of Gynecology, Woman's Medical College of Pennsylvania)

THE cases considered in this paper have been taken in straight series without selection, except for the omission of a few operations which included cholecystectomy, from the Gynecological Service of the Hospital of the Woman's Medical College of Pennsylvania and from three Gynecological Services at the Woman's Hospital of Philadelphia. They represent the work of seven surgeons. For the purpose of classification as well as possible comparison, they have been divided into five groups, namely: Simple supravaginal hysterectomy, supravaginal hysterectomy with salpingo-oophorectomy where no pelvic inflammatory disease was evident, supravaginal hysterectomy with salpingo-oophorectomy where pelvic inflammatory disease did exist, supravaginal hysterectomy with or without salpingo-oophorectomy where minor operations also were done,

or by Fullerton and Faulkner who divided their series into those cases whose postoperative temperatures never rose above 101° F., termed afebrile; those with one day of greater temperature; and those with several such days.

There were no marked differences in morbidity. Probably the morbidity in those patients who underwent partial hysterectomy which was due to infection between the layers of the broad ligaments was counterbalanced by that due to the less good preoperative condition of many of those who underwent total excision of the uterus who were older and, therefore, in general, less good operative risks. The fact that the morbidity as charted was rather lower in the group of double operations than in the others may, perhaps, be explained by the assumption that the preoperative condition here must have been considered especially good or such a prolonged procedure would not have been undertaken. It is easily understood that the morbidity of the group in which pelvic inflammatory disease was present should be greatest and most prolonged. The presence of a large percentage of appendectomies in the group of simple supravaginal hysterectomies seems to account, in part, for the higher temperature range there than might have been expected. An additional cause for this may lie in the more easily infected area about a cervical stump which has been peritonized over intervening tubal ends.

POSTOPERATIVE COMPLICATIONS

The discussion of morbidity is incomplete without special reference to definite postoperative complications. They have been listed by group and tabulated in Table III. It will be seen that the highest percentage of complications occurred among the patients who had had panhysterectomies, infected incisions leading in number. This may be slightly misleading, as any degree of stitch infection, however minor, was included. The next highest percentage occurred among the patients with pelvic inflammatory disease, demonstrating the added obstacle to a smooth convalescence presented by this reawakening of latent infection.

TABLE III. POSTOPERATIVE COMPLICATIONS

COMPLICATIONS	SUPRAVAGINAL HYSTERECTOMIES				TOTAL	PAN-HYSTERECTOMY
	WITH SALPINGO-OOPHORECTOMY			WITH MINOR OPERATIONS		
	SIMPLE	WITH P.I.D.	WITHOUT P.I.D.			
Infected incisions of any degree	3	5	1	1	10	6
Pelvic phlebitis	4	8	0	1	13	2
Phlebitis of legs	2	3	0	0	5	1
Peritonitis	0	1(f)*	1(f)	0	2	1(f)
Pleurisy	0	2	0	0	2	0
Pneumonia	2	0	0	0	2	1
Pulmonary embolism	0	1	0	0	1	1(f)
Bronchitis	2	1	0	1	4	0
Tonsillitis	1	0	0	0	1	1
Sinusitis	1	1	0	0	2	0
Intestinal obstruction	0	1(f)	0	0	1	0
Gastric dilatation	0	3(1f)	0	0	3	0
Myocarditis	0	0	1(f)	0	1	0
Cardiac failure	1(f)	1(f)	0	0	2	0
Cystitis	0	1	0	0	1	0
Pyelitis	1	0	0	0	1	0
Rectal abscess	0	1	0	0	1	0
Hematoma	0	0	1	0	1	1
Septic infection	0	0	1(f)	0	1	0
Secondary hemorrhage	1	0	0	0	1	0
Cellulitis of space of Retzius	1	0	0	0	1	0
Acute psychosis	0	0	0	1(f)	1	0
Percentage	24.0	30.2	10.8	11.4	19.1	31.8

*f, fatal.

In the group of panhysterectomies, the average age was higher than that in any other group, being 50 years, explained, no doubt, by the greater percentage of carcinoma of the body of the uterus. Here 40 of the 44 patients were white. The sedimentation time averaged 122 minutes. In 7 cases the appendages were not removed. There were 3 appendectomies. The average operative time was 96 minutes, next longest to the time of the combined minor and major operations.

INDICATIONS FOR OPERATIONS

The most frequent indication for operation was myoma uteri. There were 252 such cases. An analysis by groups is given in Table II. Sixty-seven of these were associated with cystic ovaries and 6 with carcinoma of the fundus, a per-

TABLE II. INCIDENCE OF MYOMA UTERI

TYPE OF OPERATION	TOTAL CASES	MYOMA
Supravaginal hysterectomy	79	75
Supravaginal hysterectomy with salpingo-oophorectomy <i>without</i> pelvic inflammatory disease	46	39
Supravaginal hysterectomy with salpingo-oophorectomy <i>with</i> pelvic inflammatory disease	96	89
Supravaginal hysterectomy <i>with</i> or <i>without</i> salpingo-oophorectomy with <i>minor</i> operations	35	31
Panhysterectomy	44	13

Macafee gives his percentage of myomas as 69 in a total of 122 cases; Reed and Bell give 66.6 per cent for cases on which subtotal operations were done and 24.4 per cent for cases on which total operations were done.

centage of 2.5.* There were 22 cases of malignancy of the uterus or ovaries not associated with myomas, 5 cases of procidentia, 4 of adherent retroversion, 2 of ovarian cyst, 8 of pelvic inflammatory disease, 2 of tears of the fundus, 2 of adenomatous polyps of the uterus, 1 of a pregnant incarcerated uterus, 1 of pelvic tuberculosis, and 1 of dysfunctional uterine bleeding.

LABORATORY FINDINGS, ETC.

In the whole series, the average preoperative hemoglobin was 67 per cent. The average white blood count was 7,386. The blood Wassermanns recorded were 24 positive and 127 negative. This leaves a large percentage, occurring chiefly among the earlier cases of the series, unregistered. It should be noted also that sedimentation times referred to in an earlier paragraph were not done in all cases but totaled 121 for the whole series.

The youngest patient of all those operated upon was 23 years old, the oldest 70. The average day of discharge varied little from group to group and so may be given for the whole series. It was 17.2 days postoperative.

MORBIDITY

In a series of this size it is difficult to draw any striking conclusions concerning the postoperative morbidity as indicated by the temperature curves. It was worked out for each group separately in the following manner: The low temperatures for one week, beginning the day of operation, were charted and an average drawn by the method of finding the median (i.e., the middle number for the group under consideration) for each day. The same thing was then done with the high temperatures for the day. This method, rather than that of taking the simple arithmetic average, was decided upon as a more just estimate, since it did not give undue emphasis to a few very low or very high morbidities. It seemed, moreover, a more accurate and graphic method of presenting postoperative morbidities than that recommended by Reed and Bell, who considered a case morbid if she was kept more than twenty-one days in the hospital after supravaginal hysterectomy and more than twenty-five days after panhysterectomy;

*Cf. Grave's figure of 2.0 per cent and Kelly and Cullen's of 1.7 per cent.

vaginal hysterectomy. Since it does not, however, take into consideration the delayed morbidity and mortality due to residual or subsequent lesions of the cervical stump, it, therefore, does not pretend to settle the problem as to whether subtotal or total hysterectomy is the operation of choice.

It is submitted, therefore, as a small contribution to the discussion of this subject.

REFERENCES

Macafee, C. H. G.: J. Obst. & Gynaec. Brit. Emp. 41: 333, 1934. Davis and Cuside: J. A. M. A. 19: 246, 1930. Fullerton, Wm. D., and Faulkner, Robert L.: Ibid. 95: 1563, 1930. Reed, C. D., and Bell, A. C.: J. Obst. & Gynaec. Brit. Emp. 40: 749, 1933. Treston: Ibid. 41: 588, 1934. Farrar, L. K. P.: Surg. Gynec. Obst. 60: 827, 1935. Spencer, H. R.: Brit. M. J. 1: 1157, 1932.

UTERINE BLEEDING IN THE LAST TRIMESTER OF PREGNANCY*

ITS DIAGNOSTIC SIGNIFICANCE AND TREATMENT

J. THORNTON WALLACE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of The Brooklyn Hospital)

IT IS a matter of common knowledge that bleeding from the uterus, occurring in the course of the last trimester of pregnancy, is usually indicative either of placenta previa or of premature separation of the placenta. In both textbooks and contemporary literature, there is a strong tendency to differentiate these two conditions by the presence or absence of pain during the bleeding. When pain accompanies the bleeding, the syndrome is generally considered to be pathognomonic of premature separation of the placenta, while in the absence of pain the bleeding is held, with about the same degree of assurance, to be due to placenta previa. Since our experience at The Brooklyn Hospital has led us to opinions sharply at variance with these concepts, we are presenting an analysis of all patients with bleeding in the later months of pregnancy treated at this institution during a ten-year period.

Following Bill's reports of about ten or twelve years ago, showing drastic reduction of both maternal and fetal mortality by the employment of cesarean section, a radical departure from formerly accepted procedures, the pendulum of obstetric opinion has swung far toward the use of that procedure in all cases of placenta previa among multiparas and primiparas alike. There has, likewise, been a similar trend in the handling of the other large group with bleeding late in pregnancy, namely, premature separation of the placenta. With modern tendencies so definitely toward this rather drastic form of treatment, it would not seem amiss to direct attention to the fact that many of our painless bleeding cases were due to varying degrees of premature separation rather than placenta previa and thus amenable to more conservative forms of treatment.

*Read at a meeting of the Brooklyn Gynecological Society, February 2, 1940.

The patients who underwent simple supravaginal hysterectomies showed more postoperative pelvic complications than did those who underwent associated salpingo-oophorectomies in the absence of pelvic inflammatory disease. This suggests a more ready origin of pelvic phlebitis when the adnexa are left in situ because of less uniform approximation of the peritoneal fold to the cervical stump and consequently more minute ooze and infection about that stump. Moreover, a large percentage of these patients were subjected to appendectomies, which increased the operating time, and, by this as well as by opening another possible channel of infection, apparently increased the incidence of postoperative morbidity. On the whole, pulmonary complications were more numerous following the supravaginal operations, thus corroborating the findings of Reed and Bell, but by no means duplicating their report, which holds pulmonary embolism responsible for one-third of the deaths following the subtotal operation.

MORTALITY

There was one death in the group of simple supravaginal hysterectomies, due to acute cardiac dilatation. Three deaths occurred in the series including salpingo-oophorectomy where there was no pelvic inflammatory disease. One of these was due to myocarditis, one to peritonitis, and one to septic infection. There were four deaths in the group including pelvic inflammatory disease, one of cardiac failure on the table, one of peritonitis, one of intestinal obstruction and peritonitis, and one of dilatation of the stomach. The only death in the series where minor operations were included was of acute psychosis in which the autopsy showed no cause of death. Among the panhysterectomies there were two deaths, one of peritonitis and pneumonia and one of pulmonary embolism.

SUMMARY AND CONCLUSIONS

This study was undertaken as a survey of the services mentioned, with the object of ascertaining the results over a space of ten years.

TABLE VI. MORTALITIES

NUMBER	GROUP	PERCENTAGE
1	Simple supravaginal hysterectomy	1.2
3	With salpingo-oophorectomy (no pelvic inflammatory disease)	6.5
4	With salpingo-oophorectomy because of pelvic inflammatory disease	4.0
1	With minor operations	2.9
	Total supravaginal operations	3.6
2	Panhysterectomies	4.5
11	Total mortality	3.7

It shows that hysterectomy, although an operation frequently performed, is by no means free from danger.

It suggests that, without complicating pelvic inflammatory disease, there is more pelvic postoperative phlebitis after supravaginal hysterectomy without salpingo-oophorectomy than with it.

It indicates also that the removal of the appendix is a procedure which adds considerably to the postoperative morbidity.

It re-emphasizes the hazards of operations on patients with pelvic inflammatory disease, even when this is chronic in type.

Although the series is not large, it seems to indicate that both primary morbidity and mortality are higher in panhysterectomy than in supra-

allowing it to contract down more tightly around the baby, thus closing off open sinuses and exerting direct pressure on the placenta, has satisfactorily controlled the bleeding in the majority of our patients. It is surprising to note that some of the modern textbooks do not even mention this form of therapy. Irving, in advocating its use, gives Polak credit for introducing it to this country from Ireland in 1931. It has been in use in The Brooklyn Hospital, to my knowledge, since 1923. We have resorted to cesarean section and hysterectomy hardly at all, feeling that in a situation desperate enough to require this operation, the patient would probably succumb from such a formidable procedure more certainly than if more conservative measures were used. In commenting on hysterectomy following cesarean section in uterine apoplexy, Irving rather aptly remarks: "The logic is not apparent which impels one to perform an operation with a 20 per cent mortality so that he may convert it into another with twice the death rate."

The cases here reported were taken from a total number of 10,217 consecutive deliveries in the ten-year period from 1928 to 1937 inclusive. There was a total of 70 cases of bleeding in the last trimester of pregnancy. This gives an incidence of 1 in 146 deliveries. Of these 70 cases, 55 were due to premature separation of the placenta and 15 to placenta previa. Of these 55 patients, 12, or 27.2 per cent, were toxic. Multiparity did not seem to play any part in producing premature separation, as less than half our cases, 23, were multiparas.

In premature placental separation, maternal mortality is reported as varying from 3 to 20 per cent. In the present series there were 6 deaths, or 10.9 per cent. In any discussion of premature separation, it should be emphasized that in some instances the detachment is so slight as to require little, if any, treatment, while in others the lesion is so extensive that it presents one of the most serious problems encountered in obstetric practice. Of our 55 cases, 28 may be classified as slight or mild, 18 as moderately severe, and 9 as very severe. We have endeavored always to make such a differentiation as the treatment varies with the degree of detachment. The membranes were ruptured and a tight abdominal binder applied in 40 out of the 55 cases. Only one cesarean section, and this without hysterectomy, was performed in this series. This was resorted to as much for toxemia as for ablatio placentae. Though the detachment undoubtedly contributed to the death of this patient, the toxemia was the main factor. It may be of interest in view of our seemingly high maternal mortality, to append a table (Table I) used by Irving to show the mortality rates in such cases when treated by cesarean section.

TABLE I

AUTHOR	CASES	DEATHS	PER CENT
Willson	21	4	19.0
Brodhead	8	3	37.4
Williams	10	3	30.0
Fitzgibbon	4	1	25.0
Davis	29	4	13.8
Siegel	11	2	18.2
Average	83	17	20.5

Gross fetal mortality in premature separation of the placenta is, from the very nature of the condition and the oftentimes questionable viability of the baby, necessarily high. The average of the figures reported by six authors is 73 per cent. In our series it is approximately 71 per cent.

Just as the authors of textbooks and articles have emphasized the importance of absence of pain in placenta previa, so have they stressed its presence as pathognomonic of premature separation. In discussing premature separation of the placenta, Bland states in his book: "The chief local symptom is bleeding. This is invariably associated with intense abdominal pain. We are familiar with no condition complicating pregnancy associated with a picture so strikingly characteristic. . . . A vaginal examination in order to clinch the diagnosis is not necessary in the face of symptoms so highly suggestive." McGlinn and Harer of Philadelphia comment: "It is not safe to permit any woman in whom a diagnosis of abruptio placentae has been made to remain undelivered for any considerable length of time, even in the absence of clinical evidence of profuse hemorrhage." While the above quotations represent the more radical and extreme views expressed in textbooks and literature, nevertheless, the sentiment in all I reviewed, leaned very strongly in that direction. Particularly surprising was the almost unanimous preference expressed in textbooks for cesarean section in even moderate degrees of premature separation.

Just as painless bleeding was not invariably associated with placenta previa in our series, premature separation was not always accompanied by pain. Had we followed the policy of radical intervention early in the majority of our cases, we would feel that we had needlessly subjected a goodly number of patients to the added hazards inherent in the initial and subsequent cesarean sections. Nor does the added danger of abdominal delivery over delivery from below at the first section tell the whole story. Some of these patients will develop adhesions, intestinal obstruction, rupture of the scar and may die during or following operation for these conditions. It is only when this secondary mortality is added to the primary that we may be able accurately to compare results in delivery from above and below.

It has been the policy of our service carefully to individualize each case and use those methods in the handling of it which seemed best suited to that case. Many outstanding men feel that these cases demand immediate diagnosis as to the cause of bleeding and immediate institution of treatment. They state quite categorically that there is no expectant treatment of placenta previa or premature separation of the placenta. With neither of these opinions are we in complete accord. Frequently we abstain from examining a patient who has bled but is no longer bleeding, occasionally even for several days, thus allowing the patient to re-establish her hemic equilibrium. Some of these patients may even be safely carried to viability of the child. We cannot agree that cesarean section without vaginal examination is indicated in all instances of painless bleeding. While such examination should be done only after all preparations for transfusion have been completed, it will definitely differentiate between painless premature separation and placenta previa, and indicate the type of previa and the state of the cervix.

In practically all cases of premature separation, it is our practice to rupture the membranes and apply a tight abdominal binder. This simple expedient, by reducing the amount of amniotic fluid in the uterus,

separation of the normally implanted placenta, frequently indicating less radical treatment than cesarean section.

2. We believe that premature separation of the placenta is usually better treated by the more conservative method of rupturing the membranes and application of a tight abdominal binder than by cesarean section.

3. We have endeavored to show that the widely accepted dictum that painless vaginal bleeding in the latter months of pregnancy is almost always indicative of placenta previa, is fallacious. Of 41 cases of painless bleeding here reported, 27, or 60.6 per cent, were due to premature separation of the placenta, rather than placenta previa.

REFERENCES

- Beck, A. C.*: Obstetrical Practice, Baltimore, 1935, Williams & Wilkins Co.
Binder, J.: AM. J. OBST. & GYNEC. 28: 92, 1934. *Bland, P. B., and Montgomery, T. L.*: Practical Obstetrics for Students and Practitioners, ed. 2, Philadelphia, 1934, F. A. Davis Co. *Davis, M. E.*: S. Clin. North America 15: 737, 1935. *DeLee, J. B.*: The Principles and Practice of Obstetrics, 6, Philadelphia, 1933, W. B. Saunders Co. *Falls, F. H.*: Radiol. Rev. & Mississippi Valley M. J. 59: 77, 1937. *Franklin, E. W.*: South. Med. & Surg. 99: 384, 1937. *Gordon, C. A.*: Am. J. Surg. 35: 442, 1937. *Irving, F. C.*: AM. J. OBST. & GYNEC. 32: 518, 1936; 34: 881, 1937. *Kellogg, F. S.*: New England J. Med. 209: 1201, 1933. *Marr, J. P.*: AM. J. OBST. & GYNEC. 29: 454, 1935. *McGlinn, J. A., and Harer, W. B.*: Ibid. 30: 226, 1935. *Ronsheim, J.*: Ibid. 32: 139, 1936. *Siegel, J. A.*: Ibid. 25: 894, 1933; 27: 889, 1934. *Smith, P. H.*: Ibid. 30: 62, 1935. *Stander, H. J.*: Williams Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Co., Inc. *Titus, P.*: The Management of Obstetric Difficulties. St. Louis, 1937, The C. V. Mosby Co. *Vaux, N. W.*: West Virginia M. J. 33: 485, 1937. *Wilson, R. A.*: AM. J. OBST. & GYNEC. 27: 713, 1934.

35-15 86TH STREET
 JACKSON HEIGHTS, N. Y.

DISCUSSION

DR. CHARLES A. GORDON.—Our experience with placenta previa has been entirely different from the experience of those at The Brooklyn Hospital.

I have recently reviewed 44 cases of placenta previa which occurred on the College Division at Kings County Hospital in the last five years. In all but 5 of these cases the history was the typical one of painless bleeding. In three of these 5 cases, pain was associated with the onset of labor. This is an entirely different picture.

The incidence of placenta previa on any service is of very little significance, for it varies for a great many different reasons. Incidence is unimportant. That placenta previa may be associated with pain is clear; that patients with separation may have no pain is clear. The separated placenta previa confuses the clinical history and the clinical picture. Low implantation of the placenta gives an atypical history, but for practical purposes it is placenta previa.

If the diagnosis is to depend upon palpation of the placenta, some cases will be missed. If the diagnosis is to be made on the history alone, that history must be very carefully taken and carefully weighed. It will be difficult to establish the thesis that the history of placenta previa is not that of painless bleeding in the last trimester.

I have left until last the discussion of the relation of pain to bleeding in ablatio placentae, in the hope that it will remain longest in your memory. It is the only original feature of this discussion. Of the 55 cases of premature separation of the placenta here reported, 27, or 49 per cent, had no pain at all either with or following the initial bleeding until the onset of labor pains. This, we feel, is a sufficiently large proportion of any obstetric complication to warrant emphasis and study. In 8 of these 27 cases, the bleeding occurred after the onset of labor but was not accompanied by any change in the character of the pains. In 8 other cases of the 27 painless separations, the condition was of sufficient gravity to warrant more than ordinary thought and concern. In 6 cases, the uterus was either tender, spastic or both, before their labors were completed. One of the 6 patients required transfusion and 1 died, showing that even the desperately ill may lack this symptom of pain, ordinarily considered a necessary feature of this entity. In 4 of the 27 cases, the hemorrhages were of the so-called concealed variety. The majority of our cases of painless separation presented a real problem in diagnosis, as the bleeding was the only indication that anything was wrong. The differential diagnosis was made by inability to palpate the placenta on vaginal examination and was later confirmed by evidence of placental separation at the time of delivery. That the painless type of premature separation is not confined to the earlier part of the last trimester when both uterus and baby are small, but may occur just before or at term, is attested by the fact that 11 patients were calculated to be at term and their babies weighed 7 or more pounds at birth. Brief summaries of 3 cases illustrating our point may be of interest:

CASE 1.—A 34-year-old para ii in the eighth month of pregnancy had a profuse hemorrhage, not associated with pain, two hours before admission. She was packed and sent to the hospital. Labor pains began soon after admission. First vaginal examination disclosed a thick, soft cervix, dilated two fingers. A smooth mass was palpated inside and between the cervix and presenting part. The uterus increased in size, became tense and tender. Labor pains were of poor quality and morphine caused temporary cessation of the pains. Vaginal oozing continued. A second vaginal examination, done seven hours after the first, revealed a cervix $3\frac{1}{2}$ fingers dilated, thin, and no placenta was felt. The membranes were ruptured and delivery soon ensued. About one quart of old, dark blood clots was expelled. Approximately half of the large placenta showed evidence of detachment. The final opinion was that the mass felt on first vaginal examination was blood clot. The final diagnosis was premature separation of the placenta.

CASE 2.—A patient, 34 years of age, a para iv, in the seventh month of pregnancy, had profuse bleeding before admission, but no pain, tenseness, or tenderness of the uterus. She was immediately transfused. Vaginal examination showed no placenta previa. The membranes were ruptured. No pains occurred for eleven days. At that time a rapid labor occurred with spontaneous delivery, the baby weighing 3 pounds 4 ounces. Large blood clots adherent to the central portion of the placenta indicated detachment at that site.

CASE 3.—A 20-year-old primipara, eight and one-half months pregnant, was admitted to the hospital one hour after the occurrence of moderate hemorrhage, without pain. The admission diagnosis was placenta previa. Examination by an attending obstetrician two hours after admission revealed a slightly tense, irritable uterus with a tender area 2 by 3 inches in the left lower quadrant, but without pain. Vaginal examination showed no evidence of placenta previa. The membranes were ruptured and a tight abdominal binder applied. Labor began two hours later with no further bleeding. Spontaneous delivery occurred five hours after rupture of the membranes. Several old blood clots were present on the maternal surface of the placenta.

SUMMARY AND CONCLUSIONS

1. It is our opinion that all patients with bleeding should be examined vaginally before cesarean section is done. This examination will definitely differentiate between placenta previa and painless premature

TABLE III. TIME FOLLOWING DELIVERY

DAYS AFTER DELIVERY	NO. OF PATIENTS
0-3	33
4-7	22
8-14	17
15-28	3

An arbitrary dose of 5 mg. of stilbestrol by mouth 3 times a day for a total of six doses was employed. The patients were encouraged to drink liquids freely. Tight breast binders were not employed, laxatives were ordered only for constipation, and the time-honored application of warm camphorated oil was omitted.

RESULTS

Our results following this routine were indeed gratifying. In no case did the breasts fail to become soft within twenty-four to thirty-six hours if lactation had commenced. The usual tenderness and pain were less pronounced and of shorter duration than with the older routine, consisting of tight binding of the breasts, saline catharsis, restricted fluids, and warm camphorated oil. In a few instances, a slight amount of secretion could be expressed at the expiry of this time. If medication was started the day after delivery, filling of the breasts could often be prevented.

We were able to follow 53 of our 75 patients for a sufficient length of time to determine the number of women in whom some degree of lactation reappeared. With the technique employed, 40 per cent of these patients had some return of lactation, usually on the fourth or fifth day after the last dose of stilbestrol. When lactation reappeared, there was less engorgement and the amount of secretion was small. These patients were given a second course of stilbestrol, 5 mg. three times in one day, and this usually sufficed to suppress lactation permanently.

Each patient in this series received a total of 30 mg. of stilbestrol within thirty-six to forty-eight hours. Two other patients (not included in this series) received 10 mg. three times a day for a total of 60 mg. Only two patients were nauseated, and these were both on the smaller dosage. In neither instance was it necessary to stop the administration of the drug. No other untoward effects were noted.

SUMMARY

Stilbestrol has been used in a series of 75 puerperal women for the purpose of inhibiting or suppressing lactation. Five milligrams of stilbestrol administered three times a day for a total of 6 doses relieved the breast engorgement, and decreased or prevented lactation in every case. In 40 per cent of 53 patients followed, there was a secondary recurrence of lactation. This was usually painless and slight in amount. Only 2 patients were nauseated in a series of 75 women receiving stilbestrol. We feel that the use of stilbestrol is an efficient and safe method of suppressing lactation early in the puerperium.

THE SUPPRESSION OF LACTATION BY STILBESTROL*

CRAIG W. MUCKLÉ, M.D., PHILADELPHIA, PA.

(From the Pennsylvania Hospital, Philadelphia Lying-In Hospital)

INHIBITION or suppression of lactation in the puerperium is frequently necessary. This procedure is usually prolonged, painful, and occasionally is difficult to accomplish. Recently we have employed a synthetic estrogenic substance for this purpose with satisfactory results.

We have administered stilbestrol orally to 75 puerperal women for the purpose of suppressing or inhibiting lactation. The duration of the pregnancies is shown in Table I.

TABLE I. DURATION OF PREGNANCIES

0-21 weeks	3
22-28 weeks	6
29-37 weeks	9
Over 37 weeks	57
Total	75

The indications for the suppression of lactation are shown in Table II.

TABLE II. INDICATIONS FOR SUPPRESSION OF LACTATION

Insufficient lactation	22
Elective	19
Neonatal death	11
Stillbirth	11
Inverted or tender nipples	6
Abnormal milk	2
Sick baby	2
Eclampsia	1
Maternal tuberculosis	1
Total	75

The majority of these women were private patients, and the indications listed are those given by the physicians in charge. Insufficient lactation was the reason given most frequently for drying the breasts. A number of these patients were able to provide only from one-half to one ounce at each nursing, but had firm and painful breasts. These women were considered as having "insufficient lactation." While such breasts can often be dried by the usual methods without great difficulty, the patients are more comfortable and the period of lactation is shortened if stilbestrol is employed.

The number of days following delivery before the administration of stilbestrol was started is shown in Table III.

*Read at a meeting of the Philadelphia Obstetrical Society, March 7, 1940.

TABLE I. CLINICAL RESULTS

	NO.	RELIEF	PARTIAL RELIEF	NO RELIEF	USUAL DOSE
Menstruating	13	8	3	2	0.1 to 1 mg.
Spontaneous menopause	17	13	3	1	1 mg.
Surgical or radiologic menopause	38	26	5	7	1 to 3 mg.
Total	68	47	11	10	
Per cent		69	16	15	

ment varied according to the severity of the symptoms and the nervous stability of the patient. Occasionally, permanent relief followed treatment of four to eight weeks' duration. More often it was necessary gradually to diminish the dose over a period of weeks until estrogen was no longer required and mild barbiturates maintained comfort.

SIDE EFFECTS

As to the local effects of the drug, an estrus or squamous type of vaginal epithelial response appeared usually, although the relief of flushes occurred frequently at lower dosage than did the vaginal changes.

Recurrence of vaginal bleeding appeared in 11 patients who had previously stopped menstruating. This followed relatively large doses of the substance as a rule, and we believe that a happy medium usually can be found between the relief of flushes and recurrence of bleeding. In no instance did the bleeding persist following cessation of therapy, and no case of malignancy was observed.

The general side effects were not startling. Little alteration was observed in the blood pressure or pulse rate. The common menopausal complaint of insomnia usually was relieved. The libido was unaltered. Preexisting vertigo was not affected, nor did the drug produce vertigo. While constipation was relieved by correction of the bowel habits, our experience indicates that stilbestrol acts as a mild laxative. The general relief of the subjective symptoms was accompanied by an improvement in the appetite and not by the development of anorexia, nausea, or vomiting. The majority of the patients stated that they felt greatly improved, and many returned voluntarily for further medication after a lapse in treatment was followed by the recurrence of menopausal symptoms.

TOXIC REACTIONS

The general acceptance of stilbestrol, which possesses the attractive features of inexpensiveness, ease of administration, and effectiveness, has been delayed because of its possible toxicity. The reports in the literature are widely divergent upon this point. The majority of investigators have not encountered a large percentage of untoward reactions. Reports of examinations of the blood and urine, and liver function tests usually have failed to reveal any deviation from normal.

We wish to thank Dr. J. A. Morrell of E. R. Squibb & Son for supplying the stilbestrol used in this study.

REFERENCES

Foss, G. L., and Phillips, P.: Brit. M. J. 2: 887, 1938. Nelson, W. O.: Am. J. Anat. 60: 341, 1937. Ramos, A. P., and Colombo, E.: Deutsche med. Wchnschr. 64: 782, 1938. Stricker, P., and Grueters: Compt. rend. Soc. d. biol. 99: 1978, 1928. Winterton, W. R., and MacGregor, T. N.: Brit. M. J. 1: 10, 1939.

STILBESTROL IN THE TREATMENT OF MENOPAUSAL SYMPTOMS*

FRANKLIN L. PAYNE, M.D., AND CRAIG WRIGHT MUCKLÉ, M.D.,
PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, University of
Pennsylvania Medical School)

THE clinical effects of stilbestrol have been reported in more than one hundred publications. These reports confirm the estrogenic properties of the substance but many of them question the safety of its therapeutic administration. Our experience further attests to its clinical effectiveness and casts doubt upon its potentialities of harm, provided it is administered conservatively.

We have used stilbestrol by oral administration in a series of 52 patients who were suffering from climacteric symptoms. There were 16 whose treatment was temporarily suspended for a number of weeks, to be resumed later. This enables us to present the results of 68 courses of treatment which varied from one to six months in duration. The patients were classed into three groups, according to the origin of the menopausal symptoms: (1) Those still having menstrual periods. (2) Those with spontaneous menopause. (3) Those with surgical or radiologic menopause. In this study we used the relief of flushes as the criterion of therapeutic effectiveness. Other general and local reactions were noted and recorded. Efforts were made to determine the minimal effective dose and to identify any untoward or toxic reactions.

It became apparent quite early that comparatively small doses were adequate. The requirements for relief seemed to vary according to the origin of the menopausal reaction. In the group in whom menstruation had not ceased, although climacteric symptoms had begun, mild doses of 0.1 mg. to 0.3 mg. per day usually were effective. For the spontaneous menopause group, the requirement increased to 1.0 mg. a day. The cases of radiologic or surgical menopause not only presented the most severe symptoms but needed the largest doses, usually requiring from 1.0 to 3.0 mg. a day (Table I).

Following an adequate initial dose, symptomatic improvement usually occurred within from four to seven days. The duration of treat-

*Read at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

smears change in these cases; did the gonadotropic substance disappear from the urine; and, finally, was it possible to overcome the 15 per cent of failures by the use of any other type of estrogenic substance?

There seems to be little doubt that stilbestrol tends to diminish lactation. Since these women discontinued nursing at the same time that the medication was begun, there were, however, two reasons for the cessation of lactation, namely the discontinuance of the stimulus to the nipple, and the drug. The fact that the lactation returned in some patients after the discontinuance of the stilbestrol is certainly an indication that the drug itself played a large part. It would however, be interesting to know if the amount of secretion could be diminished if the child continued nursing or the breasts were pumped.

The convenience and cheapness of this drug, as well as the clinical reports of its efficiency, recommend it above all the other estrogenic substances available for clinical use. The single obstacle appears to be the possibility of its toxicity, which holds up its immediate acceptance.

DR. CHARLES MAZER.—Drs. Payne and Mucklé's observations are in, the main in accord with my clinical observations on the use of stilbestrol in nearly 200 patients.

The product has the physiologic attributes of the natural estrogens and has a potency of 5,000 rat units per milligram. It is more potent when given orally than any other available estrogenic substance.

We have approached the problem of toxicity both experimentally and clinically. Clinically, we found no changes in the weight, blood pressure, basal metabolic rate, urine and blood constituents in 10 completely studied patients who have received the product over a period of three months in relatively large doses. The cholesterol content of the blood rose to an abnormal height in 2 of the 10 patients. Nausea and vomiting follow the administration of large doses, such as 2.0 mg. daily, in about 25 per cent of the patients.

Experimentally, the administration of 1.0 mg. daily for forty-two days produced no changes in any of the organs of the rabbit, but 3.0 mg. daily for forty-two days produced definite necrotic changes in the liver, spleen, and kidneys. In the rat, 0.1 mg. daily for an equal length of time produced congestion of the vital organs, and 1.0 mg. daily produced definite necrotic changes in the liver, spleen, and kidneys.

There is no doubt that stilbestrol has a much higher toxicity than the natural estrogens when the dose is computed in terms of weight and not in terms of rat units.

DR. S. LEON ISRAEL.—Drs. Payne and Mucklé's paper is one of the first on stilbestrol, which comments on the importance of using small doses.

In support of the clinical effectiveness of small quantities of stilbestrol are our own studies on castrated women at the Mount Sinai Hospital. We were interested to determine just what quantity of stilbestrol the castrated woman requires to maintain her blood and urine estrogen-content at the normal premenstrual levels. Our current investigations in 12 surgically castrated women indicate that as little as 0.1 mg. of stilbestrol taken orally twice daily maintains the blood level of estrogen at 1 M.U. per 40 c.c., and the urine level at from 15 to 20 R.U. per twenty-four-hour output in a castrated woman. This observation seems to support the viewpoint stressed by Drs. Payne and Mucklé that small doses of stilbestrol are not only less toxic but clinically effective.

DR. PHILIP F. WILLIAMS.—Drs. Shemkin and Grady of Washington gave a demonstration of the comparative effects of estrin and stilbestrol in the production of mammary cancer in susceptible mice. By the oral route stilbestrol was six times as potent in producing mammary carcinoma as the estrin. By the percutaneous route the stilbestrol was twice as potent as the estrin. According to their figures for the mouse they consider that to produce carcinoma in the human breast you would have to give 3,000,000 units once a week for twenty years if an equivalent carcinogenic effect was needed.

The recent report of the Council on Pharmacy and Chemistry of the American Medical Association contains the following statements:

"The reports . . . have indicated that for the most part the toxic reactions of stilboestrol were limited to gastro-intestinal distress in from five to fifteen per cent of the patients treated." . . . "Because the product is so potent and because the possibility of harm must be recognized, the Council is of the opinion that it should not be recognized for general use at the present time."

In our series, nausea and occasional vomiting occurred in 7 (10 per cent) of the 68 courses of treatment. This low incidence of gastro-

TABLE II

DAILY DOSAGE		CLIMACTERIC SYMPTOMS
DOSAGE MG.	NUMBER TREATED	TOXIC REACTION
0.1	9	1
0.2	5	1
0.3	6	0
0.5	3	0
1.0	35	4
2.0	10	1
Total	68	7

intestinal disturbance probably is due to the use of much smaller dosage than that which has been employed previously. None of our patients developed skin lesions, or exhibited signs of liver damage, although liver function tests were not done. There was no diarrhea, and no other deleterious effects were noted.

SUMMARY AND IMPRESSIONS

Stilbestrol has been administered to a series of 68 patients suffering from menopausal symptoms. Forty-seven (69 per cent) obtained complete relief, 11 (16 per cent) partial relief, and 10 (15 per cent) were not relieved by the administration of the drug. Seven (10 per cent) of the patients developed nausea or vomiting. Based upon this modest number of observations, we have gained the following impressions: Stilbestrol is estrogenic, and small quantities relieve climacteric symptoms rapidly and efficiently in the majority of patients. The most effective doses for this purpose range from 0.1 to 1.0 mg. per day. While a limited number of patients cannot tolerate stilbestrol, this intolerance appears to be manifested by minor gastrointestinal disturbances and not by major or permanent toxic effects, provided the dosage is restricted to the minimal effective requirements.

We wish to thank Dr. J. A. Morrell of E. R. Squibb and Son for supplying the stilbestrol used in this study.

DISCUSSION ON PAPERS BY MUCKLÉ, AND MUCKLÉ AND PAYNE

DR. HOWARD C. TAYLOR, JR.—The 15 per cent of reported failures in the menopausal cases are of interest. This seems to me a little higher than one might expect with the natural estrogens. I would like to know whether any studies were made to determine the reasons for the failures. Did the vaginal

THE USE OF HELIUM AND OXYGEN IN THE TREATMENT OF ASPHYXIA NEONATORUM*

PRELIMINARY COMMUNICATION

HOWARD F. KANE, A.B., M.D., F.A.C.S., WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, The George Washington University)

THE use of helium as a therapeutic gas was first suggested by Barach¹ in 1934, although in 1923 it had been employed in decompressing men working under high gas pressure.

The effectiveness of helium is due to the fact that the density of this gas is one-seventh that of nitrogen and one-eighth that of oxygen, and that it is an inert gas which can replace the inert nitrogen of air. A mixture of 80 per cent helium and 20 per cent oxygen is three times as light as air, and is, therefore, because of its greater diffusibility much more easily breathed. Barach has shown that such a mixture will pass through obstructed respiratory passages and into collapsed alveoli which are impenetrable by air.

Benedict, White, and Lee^{2, 3} found helium-oxygen to be of benefit in the treatment of the respiratory failure frequently experienced by the newborn infants of diabetic mothers. They believe that every cubic centimeter of nitrogen in air is a liability and that it can be replaced, at least theoretically, by helium. After experimenting with mixtures of various proportions, these investigators decided that the most efficient combination was 80 per cent helium and 20 per cent oxygen. This provides as much oxygen as is present in air, and if more oxygen were used it would form a heavier, less diffusible mixture. The benefit, if any, of the increased amount of oxygen would be nullified by the decrease in the penetrability of the mixture.

In view of the findings of these observers, it seemed probable that if helium would carry oxygen into partially obstructed air passages and alveoli of functioning lungs, it would act similarly in the undiluted lungs of asphyxiated newborn babies when supplied under properly controlled pressure.

In approximately 200 cases, the mixture of 80 per cent helium and 20 per cent oxygen has been employed. Few of these babies were deeply asphyxiated, some not at all. Because of the belief that every minute of delayed respiration may cause irreparable damage to brain tissue, every infant, immediately after the cord is cut, is placed in a respirator and oxygen or helium-oxygen is administered. The apparatus used is the Kreiselman modification of a resuscitator described in 1928 by Kreiselman, Kane and Swope,⁴ which delivers gas to the upper end of the trachea under controlled pressure. Several methods of evaluating the increased efficacy of the mixture over undiluted oxygen have been tried, none of which gave information of value. The experi-

*Presented at a meeting of the Washington Gynecological Society, March 23, 1940.

DR. A. E. RAKOFF.—The chief question that arises in regard to stilbestrol concerns the possible toxicity. The reports concerning its use indicate a wide variation in observed toxic effects. In our own experience, which includes observations on about 100 patients, we feel that 75 per cent can take the drug in moderate dosage without ill effect, and that the majority of the remainder will tolerate the drug after an initial period of nausea and headache.

One of the reasons for the wide prevalence of toxic effects is that too large a dose is frequently given. It should always be borne in mind that stilbestrol is a highly effective estrogen and that only in special instances is it necessary to give more than 1 mg. daily. Most patients could not afford to take an equivalent amount of a natural estrogen.

From our observations we have gained the impression, however, that a few patients have a distinct susceptibility to stilbestrol. The most severe reaction which we have found in two patients, for which no other cause could be found by the proctologist, was unexplained rectal bleeding. Another peculiar type of reaction was found in 2 patients who were receiving treatment with natural estrogens. When stilbestrol was occasionally substituted without their knowledge, they complained of severe headache and depression, and a sensation of being "drugged." They were always able to tell when they received stilbestrol rather than a natural estrogen.

A number of children with gonococcal and nonspecific vaginitis, whom we have treated with stilbestrol in a dosage of 0.2 to 1.0 mg. daily, tolerated the drug very well. There were no toxic reactions in any instance. The best therapeutic results were obtained when the drug was given in suppository form.

DR. WALT P. CONAWAY.—At a meeting of the Central Society for Clinical Research held in Chicago in November, 1939, Dr. Sevringhaus of Madison, Wisconsin, stated that with stilbestrol it was possible to get complete relief in each case tested by the oral administration. Dr. Frank Allen, of the Lahey Clinic, reported that they had used stilbestrol in 45 cases. Of his 26 carefully analyzed cases, there was definite relief in 24, but in 2 cases treatment was discontinued on account of mild toxic symptoms, such as nausea, rarely vomiting, but occasionally abdominal discomfort and marked general malaise.

DR. MUCKLÉ (closing).—Of the 68 courses of treatment, failure to obtain relief of symptoms occurred in ten instances. Seven of these failures were due to gastrointestinal symptoms which prevented maintenance of adequate dosage. In the other 3 cases, the amounts administered were insufficient in the light of our present knowledge. It is our impression that clinical relief could be obtained in every case if adequate therapy could be maintained.

Delannoy, E., and Demarez, R.: Tumors of the Internal Genitalia Among Pre-pubertal Girls, *Compt. rend. de 8^e nne Congres, Franç. de gynéc.* 30: 135, 1939.

There has not been a single report of a benign or malignant tumor of the Fallopian tube in a child. On the other hand there have been many reports of cysts of the ovary, the most common neoplasm of the genitalia in young girls. Other tumors which occur in young girls are solid tumors of the ovary, such as sarcomas, carcinomas, granulosa cell tumors, chorionepitheliomas, dysgerminomas and teratomas. Some of these neoplasms produce precocious sexual maturity. The treatment of these tumors is essentially surgical.

Tumors of the uterus in young girls before puberty are always malignant and they are rarer than ovarian growths. These uterine neoplasms consist of grapelike sarcomas of the cervix, ordinary sarcomas, squamous cell carcinomas of the cervix and adenocarcinomas. The treatment of these tumors is likewise surgical.

J. P. GREENHILL.

RENAL INSUFFICIENCY FOLLOWING TRANSFUSION OF COMPATIBLE BLOOD*

HOLLIS H. BRAINARD, M.D., NEW YORK, N. Y.

(From the Kings County Hospital)

THIS case is reported as evidence that renal insufficiency may follow transfusion of blood judged compatible by our present methods, and that the administration of alkalies as first recommended by Baker¹ to avoid this complication will not always do so. Although a few cases of renal insufficiency following the transfusion of compatible blood have been reported, it is not generally known that this may occur.

CASE REPORT

C. B., aged 30, gravida iii, para ii, was admitted to Kings County Hospital on May 31, 1939 with a history of being in active labor for five hours. Her past history was negative except for antisyphilitic treatment two years before admission.

After ten hours of active labor the patient delivered spontaneously a living full-term infant, followed by delivery of an intact placenta twenty minutes later. Profuse bleeding (about 500 c.c.) immediately followed, and despite the administration of oxytocics and vigorous massage of the fundus, the patient showed signs of shock. A 500 c.c. citrated blood transfusion (Type IV Moss) was given slowly (cross matching compatible). At the same time 15 grains of sodium bicarbonate was given by mouth every four hours. One and one-half hours after the transfusion the patient complained of a severe headache followed by a chill. The temperature was 101°F. pulse 136 and blood pressure 110/70. Five hours after delivery a large blood clot was expressed and moderately profuse hemorrhage again occurred. Blood pressure dropped to 80/60 and 1000 c.c. of citrated blood was given by drop method, over a period of three hours. Seven hours after the first transfusion, the patient's temperature was 105°F. and she showed deep jaundice. The urine was alkaline and showed many red blood cells. Two hundred and fifty cubic centimeters of 5 per cent sodium bicarbonate were given immediately intravenously. A sample of each specimen of the blood given was saved and on cross matching was found to be compatible with the patient's blood.

During the next five days the patient voided 15 to 55 c.c. of dark amber urine daily, despite an intake of 3000 c.c. of fluids each day. The daily output and corresponding blood chemistry are shown in Table I.

TABLE I. RENAL INSUFFICIENCY AFTER TRANSFUSION OF 1,500 C.C. OF BLOOD

DAY	INTAKE C.C.	OUTPUT C.C.	UREA MG.	CREAT. MG.	ICTERUS INDEX UNITS	CO ₂ VOL. %
First	2980	165	64	1.8	100	32
Second	2500	15	58	2.1	50	
Third	3000	45	58	2.5	25	88
Fifth	3000	55	115	3.8	21	55
Sixth	3000	1560	64	3.7	16	60
Seventh	4900	4110	125	6.0		
Eighth	3360	2980	120	6.0		
Tenth	5060	4525	80	5.0		
Eleventh	5945	4810	74	2.4		
Twenty-first	3360	2450	36	1.8		

The patient ran a temperature of 101° to 103° F. and on the sixth day post partum complained of pain in her right chest. X-ray examination revealed early bronchopneumonic consolidation. On the eleventh day post partum the patient began to have severe pains in her shoulder, later in her hip and knee joints.

*Read at a meeting of the Brooklyn Gynecological Society, February 2, 1940.

ments by Barach⁵ on human adults who were able to cooperate and on dogs which could be autopsied, could not be duplicated with infants as subjects. Barach's findings, based upon the study of functioning lungs, show unquestionably that helium-oxygen requires a markedly lower pressure to pass it through partially obstructed passages than do air or oxygen.

Barach⁶ also notes that "with severe obstruction the inspiratory stridor is accompanied by a sucking in of the abdominal or chest wall." This phenomenon is commonly seen in partially asphyxiated infants. "In the presence of such marked inspiratory obstruction, the secondary development of edema fluid and red corpuseles passing into the alveolar sacs contributes the dangerous factor of severe anoxemia with its resultant damaging effect on the circulatory and respiratory systems. The use of helium as a diluent facilitates the entrance of the combined gas and tends to prevent fatigue and paralysis of the respiratory musculature." After respiration has been established, therefore, it is advisable to continue the administration of helium-oxygen until the chest movements denote that breathing requires only normal muscular action.

Belief in the clinical value of the 80 per cent helium and 20 per cent oxygen mixture in the resuscitation of the asphyxiated newborn is based wholly upon the observation, perhaps biased, of 200 babies by several of the attending staff, anesthetists, the house staff, delivery room supervisors, and nurses at Garfield Hospital. All agree that in cases of light asphyxia the babies respond much more quickly to the mixture than to pure oxygen. In several cases of deep asphyxia, after oxygen alone had been used without success, the addition of helium was followed by almost immediate clearing of cyanosis and prompt respiratory movements.

The author realizes that a theory based upon experiments of others which are not exactly relevant, and upon the clinical observation of a small number of cases is practically unsupported.

The suggestion that helium be added to oxygen as a medium for initiating respiration in the asphyxiated newborn is presented, however, in the hope of stimulating further investigation of its value.

REFERENCES

- (1) Barach, A. L.: *Proc. Soc. Exper. Biol. & Med.* 32: 462, 1934. (2) Benedict, F. G., White, P., and Lee, R. C.: *AM. J. OBST. & GYN.* 39: 63, 1940. (3) *Idem*: Personal communication, 1938. (4) Kreiselman, J., Kane, H. F., and Swope, R. W.: *AM. J. OBST. & GYN.* 15: 552, 1928. (5) Barach, A. L.: *Ann. Int. Med.* 9: 739, 1935. (6) *Idem*: *J. Clin. Investigation* 15: 47, 1936.

1835 EYE STREET, N. W.

3. A variable degree of general dilatation of the tubular systems which may be marked and also involve Bowman's capsules.

4. No signs of inflammation or other significant lesions in the glomeruli.

5. As a late result a varying amount of edema and possibly chronic inflammatory infiltration of the perivascular and intertubular connective tissue.

On the basis of experimental work De Gowin⁶ and later Baker¹ have stated that renal insufficiency occurs only in the presence of an acid urine and that the administration of alkalis should prevent this complication.

Baker¹ states that no case of severe transfusion reaction has been reported where alkalis were given during the transfusion. Our patient received 15 gr. of sodium bicarbonate at the beginning of the transfusion and the first urine immediately after the reaction was alkaline. It is possible that a more serious reaction was prevented by giving alkalis in this case.

SUMMARY

1. A case of renal insufficiency is reported which occurred after transfusion of 1500 c.c. of citrated blood from the blood bank collected three days prior to the reaction. All three donors were later rechecked and their blood found compatible by typing and crossmatching.

2. Alkalis given prophylactically failed to prevent a severe transfusion reaction.

3. In our case and others reported hemolysis may occur without agglutination. Present methods of cross matching do not take this into account.

REFERENCES

- (1) Baker, S. L.: *Lancet* 232: 1390, 1937.
- (2) Bernheim, B. M.: *Blood Transfusion*, Philadelphia, 1917, J. B. Lippincott Company, p. 54.
- (3) Bordley, J.: *Arch. Int. Med.* 47: 268, 1931.
- (4) Dawson, B. E.: *Brit. M. J.* 50: 921, 1930.
- (5) De Gowin, E. L., and Baldridge, C. W.: *Am. J. M. Sc.* 188: 555, 1934.
- (6) De Gowin, E. L., Asterhagen, H. F., and Andersch, M.: *Arch. Int. Med.* 59: 432, 1937.
- (7) De Gowin, Elmer: *J. A. M. A.* 108: 296, 1937.
- (8) Goldring, William, and Graef, I.: *Arch. Int. Med.* 58: 825, 1936.
- (9) Gordon, Charles A.: *AM. J. OBST. & GYNEC.* 29: 279, 1935.
- (10) Johnson, R. A., and Conway, J. F.: *Ibid.* 26: 255, 1933.
- (11) Kolmer, J. A.: *J. A. M. A.* 73: 1459, 1919.
- (12) Levine, Philip, and Mabee, Jennie: *J. Immunol.* 8: 425, 1923.
- (13) Mason, J. B., and Mann, F. B.: *Am. J. Physiol.* 98: 181, 1931.
- (14) Moss, W. L.: *Bull. Johns Hopkins Hosp.* p. 2163, 1910.
- (15) Parr, Leland, and Kreschner, Harold: *J. A. M. A.* 98: 47, 1932.
- (16) Sharpe, John C., and Davis, Herbert H.: *J. A. M. A.* 110: 2053, 1935.

DISCUSSION

DR. CHARLES A. GORDON.—Dr. Brainard has called our attention to a very important matter. To the obstetrician, more than anyone else, transfusion is of vital importance. Time is an important factor, yet proper cross-matching is essential. It seems however, that no matter how careful we may be, severe and unexpected reactions may occur.

In 1939, on the College Division at Kings County Hospital on the gynecological service alone, we gave 444 transfusions, and there were nearly as many on obstetric patients. We had three severe reactions, two in which cross matching was accurate and rechecked, and one in which the wrong blood was used. All our transfusions are from a blood bank.

Let us not get the idea that incompatibility of blood when cross matching has been properly done is common, for it is not.

Fifteen days after the transfusion reaction the advisability of another transfusion was considered because of the patient's septic condition and hemoglobin of 30 per cent. After consultation with the Department of Medicine, the patient was given 500 c.c. of citrated blood without reaction. Four smaller transfusions were given at later dates without showing evidence of incompatibility.

Forty-five days post partum the patient continued to run an elevated temperature and showed evidence of a perirectal abscess. This was subsequently drained with remission of her temperature. The migratory polyarthralgia continued until discharge from the hospital. After three months the patient was able to walk but complained of intermittent pains in her knees and hips. X-ray examination three months post partum showed interstitial calcinosis occurring about the knee and hip joints. It is uncertain whether the transfusion reaction was responsible for this complication.

The blood transfused came from the hospital's blood bank, which has been functioning successfully since its introduction. Over 5,000 transfusions are given each year with a low incidence of reactions (7.3 per cent). The blood was cross matched by routine method, i.e., donor's cells with recipient's serum and recipient's cells with donor's serum. A competent technician is in charge of the cross matchings. The blood transfused was withdrawn from three separate donors three days prior to the transfusion. All donors were recalled after the reaction and the blood again showed compatible cross matching with the patient.

COMMENT

A few cases have been reported in which severe reactions followed the transfusion of compatible blood as determined by our present agglutination tests.

Our present method of determining compatibility is based on agglutination tests. Moss¹⁴ stated in 1910 that "Iso-agglutination may occur independently of iso-hemolysis but iso-hemolysis is probably always preceded or accompanied by iso-agglutination." Kolmer¹¹ cites Moss as having later noted instances where the sera had contained hemolysins without agglutinins. Other writers later confirmed this observation.

Bernheim² was the first to report a case of hemolytic reaction without agglutination. Goldring and Graef⁸ reported 7 cases of severe transfusion reactions and found that agglutination occurred in all but one case. De Gowin and Baldrige⁵ in 1934 reported two fatal transfusion reactions with Type IV (Moss) blood, yet cross matching had been perfectly satisfactory. Johnson and Conway¹⁰ have reported two similar cases. Gordon⁹ in 1935 reported one case where cross agglutination of donor and recipient showed compatible blood, but grouping had not been done.

All the reported cases where grouping was done were Type IV Moss. In all cases there was no apparent relationship between the amount of transfused blood and the severity of the reaction. De Gowin⁶ suggests that repeated transfusions increased the hemolytic tendency since, in the 4 cases he reviewed, the patients had repeated transfusions of varying amounts, all having had previous transfusions. The method of giving the blood does not seem to play a part in the reaction, for in the 2 cases reported by De Gowin⁷ transfusions of whole blood were given, while in the 2 reported by Goldring and Graef⁸ citrated blood was used. In our case no previous transfusion had been given and the patient had subsequent transfusions without reaction.

De Gowin and Baldrige⁵ quoting experiments by Mason and Mann showed that hemoglobin had a vasoconstrictor effect on the kidney and state, "It is as yet not possible to say whether the vasoconstrictor effect or the blocking and destruction of the tubules is the more important." Although the exact mechanism of the anuria is still uncertain, death is due to complete or partial suppression of urine preceded by intravascular hemolysis of the donor's corpuscles and a typical kidney lesion in which Baker¹ and Bordley³ summarize as follows:

1. A precipitate of hematin in the lower parts of the tubular systems extending, in some cases, into the secondary convoluted tubules.
2. Albuminous degeneration of the tubular epithelium without necrotic or fatty changes but with desquamation of some of the cells into the tubular lumina.

CASE 2.—(Dr. Irving F. Stein.) Infant B., white female, born April 12, 1938, weighing $7\frac{1}{4}$ pounds (3,300 Gm.), after a twenty-three-hour labor, by low forceps delivery. The baby was in good condition and cried spontaneously, but the head was retracted and the respirations were labored. The thyroid gland was diffusely enlarged and all three lobes were palpable. Physical findings were otherwise negative. No active treatment was instituted and after six days the thyroid gland had decreased in size by 50 per cent. The baby was gaining well, seemed quite normal, and left the hospital with the mother on the tenth day, in good condition. When seventeen days old, the baby was given $\frac{1}{20}$ gr. of thyroid extract, once daily and after three weeks of treatment the enlargement had almost entirely disappeared, only the isthmus being palpable. No enlargement whatever could be made out when the baby was four months old. The development since that time has been entirely normal.

This infant was the mother's second child. The first child was born four years previously and was normal. She was 29 years old. She was healthy and had no goiter. During both pregnancies she had been given Lugol's solution mm. x, t.i.d. from the second month to term because of tachycardia.

CASE 3.—(Dr. Henry Buxbaum.) Infant M., white male, weighing 6 pounds, 10 ounces (3,100 Gm.), born Feb. 28, 1935, after a nine-hour labor by low forceps delivery. The baby was deeply asphyxiated and resuscitated with some difficulty with a tracheal catheter. There was a large horseshoe-shaped tumor in the thyroid region, the right lobe was larger than the left. The physical findings were otherwise essentially negative. Aside from one short attack of cyanosis and some difficulty in nursing during the first few days, the infant's progress was normal. He was given no treatment and left the hospital with the mother at the end of ten days in good condition, weighing 6 pounds 8 ounces (3,000 Gm.). An x-ray examination on the second day after birth showed some compression of the trachea and a very large heart shadow which extended nearly to the left chest wall. The subsequent progress of the infant was good. The thyroid enlargement was still evident at three months though much smaller. At the age of one year the thyroid could no longer be palpated.

The mother was 32 years old, had been married fourteen years with no pregnancies until the present one. She had been healthy except that she had suffered from asthmatic attacks for the past ten years, and during the last five years had been taking large doses of potassium iodide continuously. In the fourth month of her pregnancy she had hyperemesis gravidarum from which she recovered under conservative management in the hospital.

COMMENT

Congenital goiter is very common in those parts of Europe where goiter is endemic. In certain parts of Switzerland, it was reported that one out of every two babies born had a congenital enlargement of the thyroid. In 1935 Ludwig Aschoff reported that, in Freiburg in Baden, 10 per cent of the neonatal deaths were due to congenital goiter. A goiter is present in the mother in a great majority of the previously reported cases: of the 53 cases reported by Demne, 23 had goiterous mothers; Richard's 43 cases had goiterous mothers in 23 instances. In Rübemann's 9 cases, Crattis' 7 cases, Rähäs' 11 cases, and Skinner's 14 cases, every mother had a goiter.

But not every mother who has a goiter will give birth to a child with a congenital goiter. In Rähäs' report of 11 cases, there were no instances of siblings that had had a congenital goiter. In each case, however, the mother's goiter had definitely increased in size during the pregnancy which resulted in a newborn infant with a goiter. He reported one remarkable case in which the patient was the mother's ninth child. During her previous pregnancies she had noticed no enlargement of her thyroid and had previous to that never had any semblance of a goiter. None of her other eight children had ever shown any goiter, then suddenly during her ninth pregnancy her thyroid began to enlarge and she gave birth to a child with a large congenital goiter. It would appear that in

THREE CASES OF CONGENITAL GOITER*

A. H. PARMELEE, M.D., EDWARD ALLEN, M.D., IRVING F. STEIN, M.D.,
AND HENRY BUNBAUM, M.D., CHICAGO, ILL.

THE occurrence of congenital goiter in this country is extremely rare if we are to judge from case reports in our medical literature. From the Chicago area there are no reports published in the last ten years. This is significant because this and the adjoining Great Lakes Region is considered goiter territory. In a recent article in a European medical journal, the statement is made that wherever goiter is endemic the incidence of congenital goiter constitutes an index of the severity of the endemic. If this is true, there can be very few places in America where goiter is endemic in any serious degree.

We are reporting three cases of congenital goiter not only because of the rare occurrence of the disease in this region, but also because in each instance the mother had been taking iodine throughout her pregnancy.

CASE 1.—(Dr. Edward Allen.) Infant W., a white male, born at term May 16, 1939. The delivery was spontaneous after a four-hour labor. Birth weight was 6 pounds 6¾ ounces (2,900 Gm.). Color at birth was good, but cyanosis developed rapidly and he was resuscitated with difficulty. Severe dyspnea continued and breathing seemed possible only when the head was retracted. Oxygen was administered continuously. There was a large soft horseshoe-shaped tumor occupying the thyroid region, made up of three evenly rounded lobes. The left lobe was the size of a lemon, the right somewhat smaller and the isthmus was elongated and slightly nodular. The heart was enormously enlarged, occupying almost the entire left thoracic cavity, and a loud systolic murmur was heard over the precardium. All other physical findings were essentially negative. Dyspnea continued to be severe but by keeping him in a fixed position with the shoulders elevated so that the head dropped back, and by giving oxygen continuously, his color remained fairly good. The dyspnea and recurrent attacks of cyanosis continued but became gradually less severe. After eight days his respiration was quite normal. He was given breast milk by gavage for the first two weeks. Iodine ointment was applied as an inunction to the thyroid tumor from the second to the eighth day and again from the fifteenth to the twenty-third day. There was little change in the size of the tumor until after the sixth day when its size began noticeably to decrease. By the time of his discharge from the hospital it was only about one-third its original size. The size of the heart to percussion and also by x-ray examination had also decreased. Subsequently his condition has improved steadily and when last seen at the age of eight months he weighed 17¾ pounds and was normal in every way. The heart was normal in size and the thyroid gland was barely palpable. The skin and soft tissues of the neck were somewhat loose and redundant.

In Dr. Allen's history of the mother there are several significant facts. She was 27 years old. This infant was her second child. She had always been healthy except that during her first pregnancy she began to have asthma and during the last three months of that pregnancy took potassium iodide for relief. The first child was entirely normal, had no goiter, and weighed over 9 pounds. She continued to take potassium iodide frequently from July, 1937 until May, 1939 in large doses, not bothering to measure it with a spoon but drinking it directly from the bottle. She had no visible goiter when under Dr. Allen's care, but when she brought the baby to me eight months after she had discontinued the medication she had a mildly enlarged thyroid which she said she had noticed and that it was slowly increasing in size. She came to Chicago in November, 1938 from Texas and insisted she had never had any thyroid enlargement before.

*Presented at a meeting of the Chicago Gynecological Society, February 16, 1940.

AN ACUTE CRISIS OF SUPRARENAL INSUFFICIENCY COMPLICATING PREGNANCY*

CHARLES EDWIN GALLOWAY, M.D., EVANSTON, ILL.,
DON C. SUTTON, M.D., AND JOHN ASHWORTH, M.D.,
CHICAGO, ILL.

*(From the Departments of Obstetrics and Medicine, Northwestern University
Medical School)*

THE following case report is presented to call attention to the dangers incident to disturbance of the sodium-potassium balance in the blood serum.

Mrs. H. H. W., aged 32 years, a well-nourished white woman, first consulted Dr. Galloway on March 20, 1939. She presented apparently a normal three months' pregnancy. The past history was uneventful with the exception of a laparotomy for an ovarian cyst in 1930. After the operation she remained in the hospital for two months because of wound infection, a urinary fistula, and a thrombophlebitis of the left leg.

On March 20 her weight was 125 pounds; systolic blood pressure 120. The blood count and hemoglobin determinations were within normal limits. The physical examination revealed no important defects. Until the last of July the systolic blood pressure ranged from 110 to 130.

Throughout her pregnancy she complained of frequent "spells" of weakness and faintness. About the middle of June these became more frequent and severe.

On July 18 the urine showed two-plus albumin. Because of the albuminuria a 1,200 calorie salt-free diet was ordered. The weakness and albuminuria continued until July 28 when 2.5 Gm. of potassium chloride daily was ordered. On July 30 she complained of severe headache, severe abdominal pain, nausea, weakness, and vaginal bleeding. On July 31 she entered the hospital complaining of nausea, pain in the lower abdomen and back with a referred pain to the chest and shoulders, numbness in the arms and headache. She was in extreme shock with a thready pulse of 160, cold moist skin, and blood pressure of 96/70-. Her lips and finger nails were dusky. The physical examination did not reveal a cause for her condition.

She was treated for shock with elevation of the foot of the bed, heat, and adrenalin.

She temporarily improved but within an hour relapsed, her condition became alarming, the blood pressure was then 70/58. Following the intravenous administration of 1,000 c.c. of 5 per cent glucose in Ringer's solution, she improved and the blood pressure rose to 114/60.

Blood chemistry done on August 1 showed urea, 4.81 mg. per cent; uric acid, 2.5 mg. per cent; and chlorides, 494 mg. per cent. On August 2 the serum albumin was 3.88 per cent and globulin 1.77 per cent. Her condition remained the same with the blood pressure ranging from 110/60 to 95/60.

On August 5 she was seen by Dr. Sutton, when she had a pulse of 132 and a blood pressure of 95/60. An Ewald test meal revealed free hydrochloric acid 12 and total acidity 20, the basal metabolic rate was -4. The potassium chloride was discontinued and a full salt diet allowed, and an additional 2 Gm. of NaCl were given daily. The next seven days she remained weak, the pulse continued rapid, average 120, and the blood pressure varied from a systolic of 85 to 110. Beginning August 12 she was given 2 c.c. of suprarenal cortical extract daily and was allowed to leave the hospital August 18.

She remained at home until September 26 and continued on the same salt ration. A total of 10 c.c. of suprarenal cortical extract was given during the inter-

*Read at a meeting of the Chicago Gynecological Society. March 15, 1940.

this last pregnancy some endogenous or exogenous factor disturbed her endocrine glands, she developed a pathologic enlargement of the thyroid and simultaneously there developed a goiter in the fetus. The etiology of the goiter in the fetus seems closely bound up with the factor or factors that caused the goiterous enlargement of the mother's thyroid. It must also be admitted, of course, that many mothers develop a goiter during pregnancy and the infant born does not have a goiter.

The three theories advanced to explain congenital goiter are: (1) heredity, (2) infection, (3) iodine deficiency. Heredity can probably not be ruled out, at least it would seem to be a contributing cause. Infection can probably be dismissed. As for iodine deficiency, there can no longer be any doubt of its enormous significance, whether or not it can be proved to be the primary cause. In Switzerland, where the use of iodized salt as prophylaxis is now obligatory, congenital goiter is rapidly becoming a rare clinical picture. Eggenberger now believes there is little support for the theory of heredity. A mother may have ever so large a goiter, but, if she takes iodized salt regularly during her pregnancy, she will never have a goiterous infant, he says.

Now, how are we going to explain the goiterous infants of these three mothers who all took iodine in large doses during their pregnancy? None of these three mothers had goiters but their newborn infants did. Aschoff says the etiology is closely bound up with the general metabolic condition of the mother. Hormonal disturbances of the mother may produce changes in the fetus which lead to thyroid enlargement. Thyrotropic hormones from the pituitary gland may be responsible. In our cases was the large amount of iodine ingested responsible for some profound metabolic disturbance, or endocrine imbalance?

Curtis and Puppel have shown that in exophthalmic goiter there is an increased mobilization and elimination of the body iodine, so that the patient may be in a negative iodine balance during certain stages of the disease even in the presence of a normally adequate intake of iodine. They further state that it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and is compensatory in an attempt to meet a continued bodily demand for utilizable iodine after the store of utilizable iodine has been depleted. "There is a striking similarity between the disturbed iodine metabolism in hyperthyroidism and the disturbed calcium metabolism of hyperparathyroidism." This similarity also extends to the disturbed sugar metabolism of diabetes.

Perhaps we may liken the hyperplasia of the fetal thyroid in these cases to the hyperplasia that occurs in islet tissue of the pancreas in the infants born of diabetic mothers. The etiologic significance, if any, of the iodine medication in these cases is still undetermined and we are anxious to have your suggestions.

55 WASHINGTON STREET

Arenas, N., and Echegaray, E. M.: Homolateral Hematometra and Hematosalpinx in a Case of Uterus Duplex, *Rev. méd. latino-am.* 25: 297, 1939.

The authors review the literature of hematosalpinx and hematometra and present an interesting case of a 13-year-old girl in whom torsion of an ovarian cyst was suspected. She had suffered from increasing dysmenorrhea and abdominal colic since the menarche at the age of 12. At laparotomy, a left hematosalpinx was found and removed. The duplex uterus was noted each with its tube, round ligament, and ovary. Postoperative lipiodol study showed the right uterus to be permeable and revealed the presence of a right hydrosalpinx. The left uterus, which was atretic at the cervix, was removed at a second operation. The authors call attention to the importance of the symptom of dysmenorrhea, which is found in 95 per cent of cases of hematosalpinx, especially when accompanied by a palpable tumor in the tuboovarian region.

R. J. WEISSMAN.

FILM SCALES FOR USE IN PELVIMETRIC ROENTGENOGRAPHY*

J. BAY JACOBS, M.D., F.A.C.S., WASHINGTON, D. C.

(From the Department of Obstetrics, Georgetown University, and the Bureau of Maternal Welfare, Health Department, District of Columbia)

IN 1936 I presented in detail before the Radiological Society of North America,¹ some of the standard techniques of roentgenographic pelvimetry and commented rather freely upon the merits of each. Since then, I have encountered several hundred borderline pelvises and have measured them by my simplified method of lateral roentgenography. It is the purpose of this paper once more to direct attention to the importance of x-ray pelvimetry and to present a modification in technique which yields many advantages.

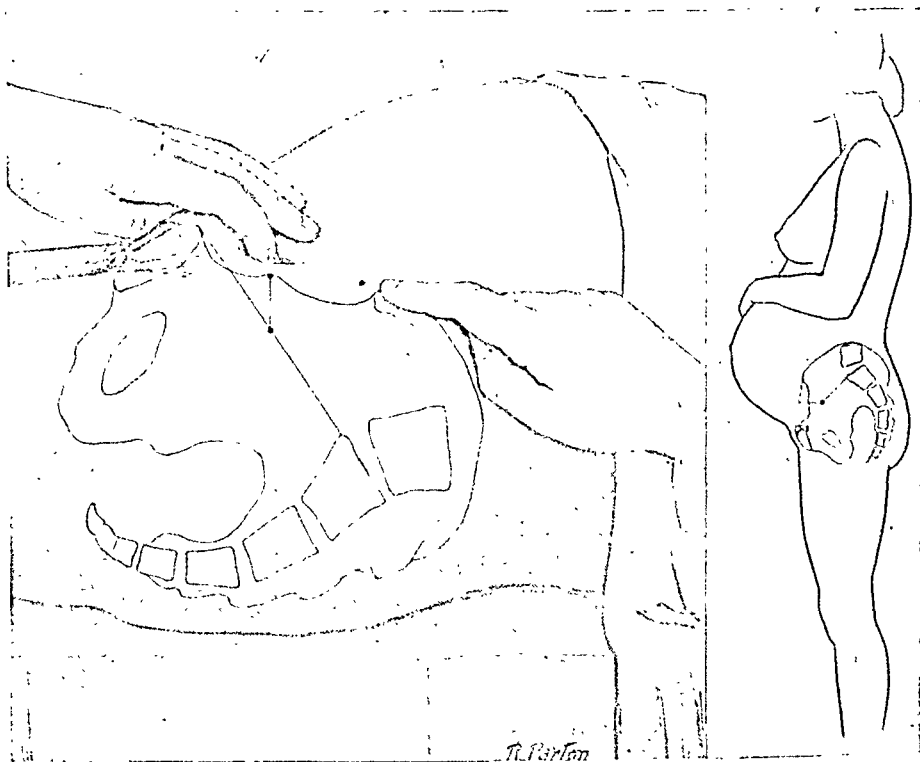


Fig. 1.—After locating the anterior superior iliac spine, pressure is made over the location of the anterior inferior iliac spine. The approximate middle of the true conjugate diameter lies one inch below this point when patient is in recumbent posture, or one inch posterior to it in standing posture.

One who has devoted much time to this phase of obstetrics is naturally gratified to note the increasing interest that is being shown by obstetricians and roentgenologists. Many more practitioners would utilize roentgenographic pelvimetry if they were familiar with a simple, reliable procedure. The fact that many methods are used and advocated increases confusion, since most men are unable to evaluate comparative advantages.

Distinction should be made between the two general types of x-ray pelvimetry; namely, (1) anteroposterior, and (2) lateral.

*Received for publication, Jan. 30, 1940.

val, nevertheless, she was practically bedridden, although the blood pressure maintained an average of 110/70. The albuminuria gradually disappeared.

September 26 she returned to the hospital to await her confinement. During the time preceding delivery she was in bed on a full diet to which 8 Gm. of NaCl was added daily. During this period she continued weak and complained a great deal of abdominal pain. The blood pressure continued above 105 mm. mercury.

After an uneventful labor she delivered a 3,370 Gm. female child. Immediately following labor she was given 1,000 c.c. of normal saline solution intravenously, and 2 c.c. of suprarenal cortical extract intramuscularly. A total of 8 c.c. of suprarenal cortical extract were given on both August 13 and 14, 6 c.c. on August 15 and 16, and 2 c.c. on August 17.

On October 18 she complained of extreme headache which was relieved only by $\frac{1}{4}$ gr. of morphine, hypodermically. At noon her blood pressure was 150/80 and 170/80 at 6 P.M.

On October 19 she received $\frac{1}{4}$ gr. of papaverine and on October 20 1 gr. was given at four-hour intervals for three doses and 1 gr. on October 21. The blood pressure gradually fell to 118/60 on October 22.

She returned home well, and on December 20 she had a blood pressure of 138/75. Her urine has shown no albumin. She feels well and is taking care of her apartment and baby without help.

This patient presents two interesting syndromes; namely, a typical Addisonian crisis followed later by an acute episode of hypertension.

The story of weakness and faintness followed by a crisis, the important symptoms of which were abdominal pain, nausea, collapse with extremely low blood pressure and rapid pulse, is readily ascribed to a crisis of Addison's disease. During the period preceding the onset of the crisis she was placed upon salt restrictions quite similar to that of a Wilder test for Addison's disease and in addition was given a total of possibly 6 Gm. of potassium daily. The estimate of potassium is based upon the assumption that the average diet contains 4 Gm. of potassium daily.

Although no pigmentation of the skin was found, the story of weakness, abdominal pain, and the reaction to a disturbance of the Na-K equilibrium, serve as evidence for the diagnosis of an insufficiency of the suprarenal cortex.

Subsequent events suggest that insufficiency of the suprarenal cortex was a temporary one during pregnancy. The cause of such an insufficiency is at best conjectural.

A logical assumption would be that as the result of the pregnancy the balance of the glands of internal secretion was disturbed.

The episode of hypertension can only be explained as an overactivity of the suprarenal glands with the cessation of pregnancy. The cortical extract used did not have a detectable quantity of epinephrin.

Even allowing that the diagnosis of suprarenal insufficiency is doubtful and the explanation of its cause more so, the case is still important, as it calls attention to the dangers incident to the disturbance of the Na-K equilibrium.

30 NORTH MICHIGAN AVENUE

Amolsch, Arthur L.: Congenital Atresia of the Tricuspid Valve Complicated by Congenital Myxosarcoma of the Labium Majus, Arch. Path. 24: 777, 1937.

Amolsch reports a case of primary congenital atresia of the tricuspid valve in an infant who died at the age of four months, bringing the total number of such reported cases to 45. The clinical symptoms were intermittent cyanosis, dyspnea, increased respiratory rate, and polycythemia. The clinical findings consisted of cardiac enlargement to the left, dilated right auricle, and a systolic murmur in the third intercostal space. The cardiac enlargement was borne out at autopsy. Another interesting finding was a congenital myxosarcoma of the left labium majus. This tumor was removed at the age of one month. Metastases to the lungs resulted.

WILLIAM B. SERBIN.

A brief description of the procedure is warranted. With the patient in the recumbent posture, the doctor stands at her left side and places his right index finger upon her left anterior superior iliac spine, while the index finger of his left hand is passed downward along Poupart's ligament to the approximate location (distance of about two inches) of the left anterior inferior iliac spine. Pressure is made over this point. With the aid of a skin pencil, the station of this landmark (anterior inferior iliac spine) is lightly indicated on the lateral aspect of the patient's left hip. The approximate middle of the true conjugate diameter lies one inch below this point, and should be designated by a darker spot (one inch below light spot).

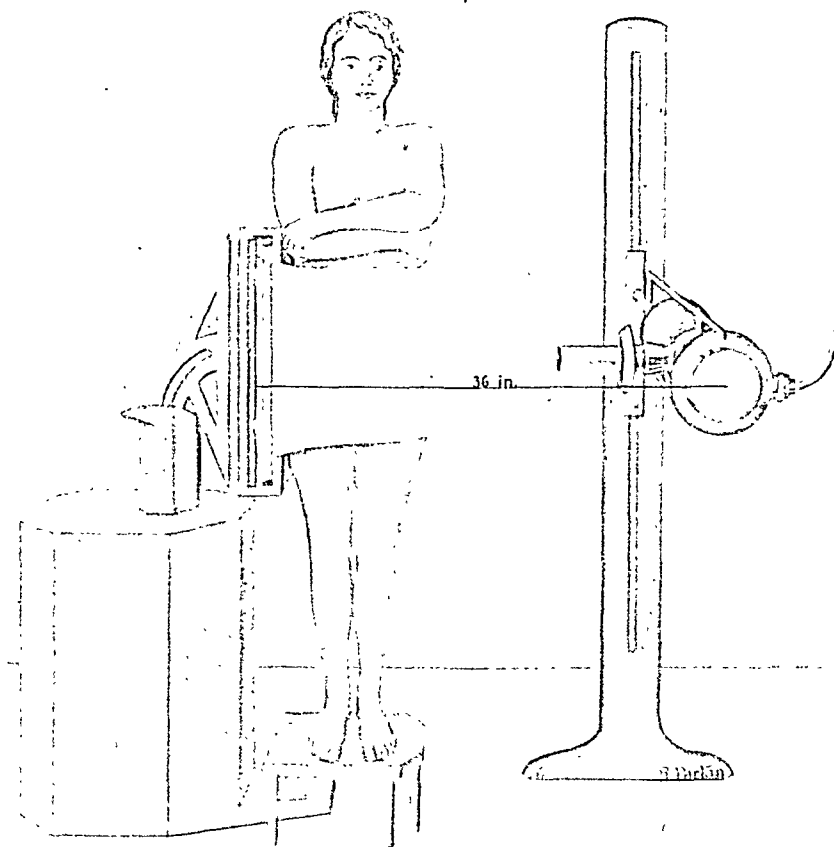


Fig. 3.—Patient secured in position and target of tube directed over the point denoting the approximate middle of true conjugate diameter.

Patient is now made to stand with right hip in contact with an adjustable vertical Bucky diaphragm. While applying moderate pressure to her left hip, the physician measures the distance from genital crease (plane of true conjugate diameter) to film, which is situated one inch behind the surface of the Bucky diaphragm. This is the "inlet-to-film" distance.

He then faces patient's left side, and sights her thighs, in order to have one hip directly over the other.

The target of the x-ray tube at a fixed distance of 36 inches from the film is directed over the dark spot on patient's left hip. Before exposure is made, patient is secured in position with the canvas binder that is routinely used by roentgenologists.

After extensive experience with the above procedure, I have found that the "inlet (genital crease)-to-film" distance varies from six to eight and one-half

My technique of anteroposterior roentgenography,^{2,3} although accurate, has the disadvantage of being rather technical and, for that reason, has not gained wide acceptance. The view of the inlet, obtained by anteroposterior roentgenography, possesses two features that are lacking in lateral roentgenography. These are the ability to measure the transverse diameter of the inlet, and to observe the contour of the pelvic brim.

The lateral technique, although lacking in these two respects, yields numerous other facts of importance, and is rapidly stimulating interest for the following reasons: (1) The procedure is inexpensive since it requires the use of only one film. (2) The method is very simple. (3) There is no inconvenience to the patient or doctor. (4) No elaborate apparatus is required. (5) The obstetrician or roentgenologist need not be especially skilled. (6) Important landmarks are readily distinguishable. (7) The topography of the pelvis is visualized and dis-

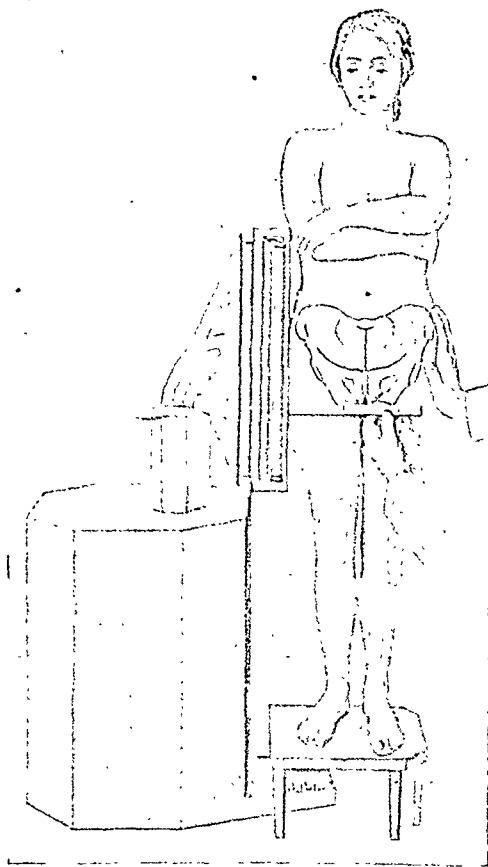


Fig. 2.—While making moderate pressure over patient's left hip, the distance from genital crease to surface of Bucky is measured. Since film is situated one inch behind this surface, one inch must be added, in order to obtain the true conjugate (inlet) -to-film distance.

crepancies from normal that may affect the mechanism of labor are easily discerned. (8) Pictures might readily be taken at term or even in labor, and accurate determinations arrived at. Such views permit not only mensuration of cephalic and pelvic diameters, but also permit a rather dependable interpretation of the relationship between the fetal skull and pelvic inlet. (9) Pelvic inclination may be noted. In this respect I shall subsequently direct attention to the usual method of engagement. (10) I know of no other method, regardless of complexity, that may yield more prognostic information than the simple technique here proposed, with the use of only one film.

distance. After the film is developed and dry, the film strip that corresponds to the "inlet-to-film" distance is superimposed, and the true conjugate diameter measured by counting the dots between the middle of upper border of symphysis and sacral promontory. Using the same film strip, the presenting diameter of the fetal skull may be measured.

Much information to be gained from interpretation of the lateral pelvic roentgenogram has already been discussed.⁴ I wish to direct attention here to the method of engagement of the fetal skull as viewed from the lateral aspect in the standing posture.

It is important to realize that when the pregnant woman stands, the presenting part of the fetus is more closely approximated to the pelvic brim. This permits of a fair comparison of the size of the fetal head and the true conjugate diameter. Disproportion is readily detected in many cases regardless of lineal determinations.

Also when the head is in contact with, or in, the brim, this pelvimetric technique yields reliable measurement of the presenting diameter of the fetal skull.

A head that falls away from the brim when the mother lies on her side has a tendency to enter or dip into the inlet when she stands.

In a remarkably high percentage of cases the biparietal enters the true conjugate diameter.

After working with Garnett⁵ on pelvic inclination, my curiosity was aroused as to the method of engagement in cases of faulty inclination. It is surprising to observe that in the vast majority of such patients engagement occurs before term, the head making a right-angled turn on the spinal column in order to enter the inlet. This particular attitude on the part of the fetus is noteworthy.

CONCLUSION

A simple, inexpensive, accurate technique of pelvimetric roentgenography, which the author has found to be of unusual practical value in the management of several hundred borderline cases, is presented.

It is universally recognized that there actually exists an urgent need for the widespread use of x-ray pelvimetry.

Realizing that any procedure accepted for such general use, especially where the majority of men are not technically trained, must be one that will yield uniform readings in the hands of all practitioners, so as to afford a greater degree of standardization in prognostication of the patient with a borderline pelvis, I have presented the technique described with the hope that it may be generally adopted.

Film scales are manufactured and sold by Bastion Bros., Rochester, N. Y.

REFERENCES

- (1) *Jacobs, J. Bay*: Radiology 28: 406, 1937. (2) *Idem*: South. M. J. 25: 828, 1932. (3) *Idem*: AM. J. OBST. & GYNEC. 32: 76, 1936. (4) *Idem*: Ibid. 28: 227, 1934. (5) *Garnett, A. F. P., and Jacobs, J. Bay*: Ibid. 31: 388, 1936.

WASHINGTON MEDICAL BUILDING.

inches in different women. So with the aid of the usual lead grid, having perforations 1 cm. apart throughout its surface, a series of film strips were prepared by placing the target of the tube 36 inches from a blank film, and interposing the lead grid 6 inches from the film, and taking a flash exposure. This film, after being developed, then becomes the 6 inch scale and may be used for computing measure-

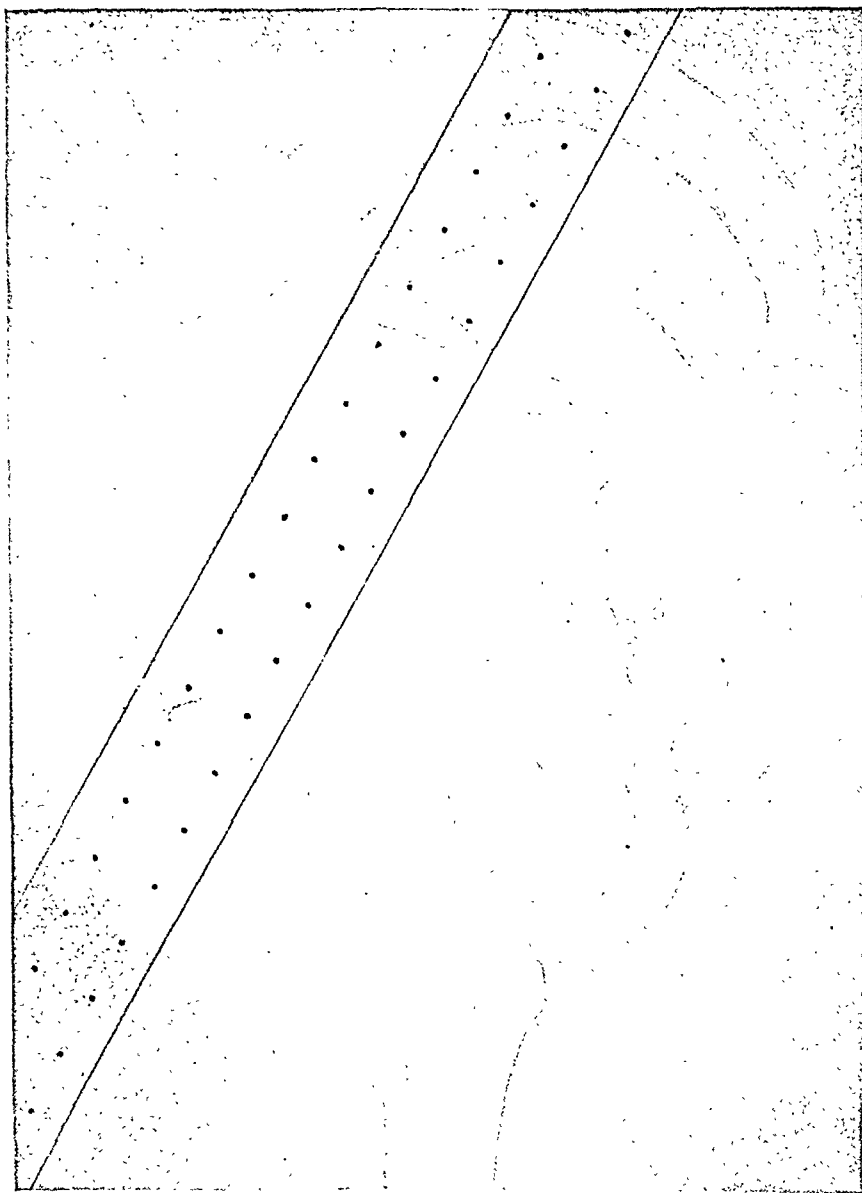


Fig. 4.—When the appropriate film scale is superimposed on the developed film, pelvic and cephalic diameters are readily measured.

ments on the film of any woman in whom the "inlet-to-film" distance is 6 inches. Similarly a film strip is prepared with the grid $6\frac{1}{4}$ inches from a film; another at a distance of $6\frac{1}{2}$ inches; another at $6\frac{3}{4}$ inches and so on, up to $8\frac{1}{2}$ inches, giving a set of eleven film scales. Each should be properly labeled.

The technique of pelvimetric roentgenography thus becomes simplified and less expensive, since all one need do is to take pictures at a fixed distance of 36 inches from target to film, and note the "inlet (genital crease)-to-film"

normal period occurred Nov. 25 to 29, 1937. On December 20 she had what she regarded a normal period except that its duration was seven days. After an interval of two days, bleeding recurred for another seven-day period. Following this there was daily spotting of reddish brown blood until the onset of the present illness. Two weeks before admission the patient had an attack of nausea, vomiting, and moderate pain in the right lower abdomen which she did not consider serious enough to mention to her physician who treated her at that time for an upper respiratory infection. It was impossible to learn any facts which enabled us to estimate the duration of the pregnancy on the opposite side or to determine when impregnation had occurred. This experience is similar to that related in most of the other reports regarding this unusual condition.

The title of this paper is not meant to imply that the two pregnancies were viable simultaneously but that impregnation must have occurred in each tube within a comparatively short interval of time. The title is intended to convey the fact that impregnation occurred in the right tube before the pregnancy in the left tube had undergone complete resolution.

REMOVAL OF A GRÄFENBURG RING WITHOUT INTERRUPTION OF PREGNANCY*

ROBERT A. KIMBROUGH, JR., M.D., AND PENDLETON TOMPKINS, M.D.,
PHILADELPHIA, PA.

THE Gräfenburg ring is a closely coiled spiral of fine silver or gold wire curved to form a ring 1.5 to 3 cm. in diameter. When placed within the uterine cavity this device decreases fertility. It is not a contraceptive, because it does not prevent, although it may interfere with union of the sperm and ovum. It is a means of birth control, because it may prevent nidation of the fertilized ovum, or it may act as an abortifacient if nidation does occur. The Gräfenburg ring has been used extensively abroad, less frequently in this country. It is an unsatisfactory instrument because it does not prevent intra- or extrauterine pregnancy, it predisposes to pelvic infection, it may perforate the uterus, and it may be lost without the patient's knowledge. For these reasons, based upon dozens of unfavorable reports, the use of an intrauterine foreign body (Gräfenburg ring, gold stem pessary, Pust star, etc.) as a "contraceptive," is regarded as dangerous practice if not malpractice.

The following report is made because no similar case was discovered in a review of some 50 publications on the Gräfenburg ring.

Mrs. A. S., aged 33, gravida iii, para i, reported for prenatal care on Nov. 4, 1938, eight weeks after her last menstrual period. She was married in 1929, was delivered spontaneously of a normal infant in 1930, and in 1931 consulted Dr. Ernst von Gräfenburg for contraceptive advice. He fitted her with an intrauterine silver ring. Each year thereafter he saw the patient and removed the ring for a period of four weeks. During the rest of the year the ring was worn continuously. He used three different rings. The first, of silver, was removed because of abdominal pain. The second ring, of gold, "slipped" and was replaced on March 5, 1935 by a larger coiled gold ring which was worn continuously until November, 1938. The patient considered the Gräfenburg ring an ideal contraceptive although 2 pregnancies had occurred, one ending by miscarriage at the eighth week and the present one.

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

SUCCESSIVE, COEXISTENT TUBAL PREGNANCIES*

CHARLES A. BEHNEY, M.D., AND WILLIAM J. HANES, M.D.,
PHILADELPHIA, PA.

MULTIPLE pregnancies, at least one of which is tubal, are rare enough to be a medical curiosity. Bilateral tubal impregnation is still less frequent, and according to Fishback only 76 such cases have been reported in the literature (1939). Our case and one reported by Torpin in a recent issue of this JOURNAL makes a total of 78 cases. This finding, seldom recognized before operation, is of some practical importance in that it illustrates the necessity of inspecting both adnexa at the time of operation.

On Jan. 19, 1938, at 7:00 A.M., an unmarried white woman (E. E.), aged 25, on awaking, noted generalized lower abdominal pain, more severe on the right side and radiating to the back. She felt weak, vomited, and had a fruitless desire to defecate. At 9:00 A.M. one of us (W. J. H.) found her in shock, with a rigid abdomen, and the classical symptoms of severe intra-abdominal hemorrhage. Her blood pressure was 60/40, pulse 140, temperature 97° F., and respirations 40. Both pupils were dilated. There was exquisite tenderness over the entire abdomen, more marked on the right side. Shifting dullness in both flanks and a bulging cul-de-sac were noted. On rectal examination a tender mass 3 cm. in diameter was felt in the midline behind the uterus.

At 9:30 A.M. she was admitted to the Bryn Mawr Hospital by ambulance and was immediately prepared and examined vaginally. A diagnosis of ruptured left tubal pregnancy with severe intra-abdominal hemorrhage was made. She was immediately taken to the operating room and a lower abdominal midline incision was made, while transfusion from a supply of banked blood was begun.

The peritoneal cavity was full of blood. The left adnexa were delivered and the mass which had been palpated preoperatively was inspected. It had the typical gross appearance of an unruptured tubal pregnancy. Since there was no bleeding in this situation, the condition of the opposite tube was immediately investigated. The distal one-third of the right tube opposite its mesosalpinx was ruptured for a distance of 3 cm. An effort at clotting had taken place and in the partially formed clot a fetus (5 cm. in length) was lying. The shattered tube was removed in the routine manner and the left tube excised immediately afterward. The round ligaments were quickly shortened and the abdomen closed in layers while the blood transfusion was completed. After an uneventful convalescence and primary union of the incision, the patient was discharged from the hospital on Feb. 2, 1938.

The following is the pathologic description of the tissue removed: The walls of the ruptured right tube were distended, thickened, and infiltrated with chorionic villi and blood. Section showed hyperplasia of the muscular elements, with edema and lymphocytic infiltration. Part of the mucosa was replaced by decidual tissue; in other parts it was hyperplastic. The fetus was 5 cm. long and microscopic examination showed it in a state of good preservation.

The left tube was dilated in its middle portion and contained an organized clot 15 mm. in diameter. Microscopic examination showed moderate hyperplasia of the mucosa of the tube. The contents, consisting of clotted blood, showed areas of necrosis, fibrous tissue interspersed among fairly well-preserved placental tissue and decidua, with infiltration of polymorphonuclear leucocytes.

After the convalescence had progressed satisfactorily, the following information, previously unknown, was obtained from the patient. Her past medical history was irrelevant, in no way suggestive of previous pelvic disease. The last

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

RADIUM THERAPY IN GYNECOLOGY

GEORGE GRAY WARD, M.D., F.A.C.S., F.R.C.O.G. (HON.),
NEW YORK, N. Y.

(From the Woman's Hospital)

THE radiologist has invaded many fields in gynecology which, formerly, were largely amenable to surgery only, so that today radium and x-ray are firmly established as essentials in the gynecologic armamentarium. Consequently, it is obligatory for the gynecologist to be familiar with the use of these modalities.

This discussion will be confined to the use of radium in gynecology and will refer only to x-ray therapy as an adjunct. Radium is used in gynecology to treat benign and malignant neoplasms and certain functional disorders. In order to employ radium safely and efficiently, its effect upon normal and malignant tissues must be understood, and the dangers and possible complications resulting from its use must be fully appreciated. This implies a knowledge of the dosage and screening necessary to accomplish the result desired.

It is the effect of the gamma rays, given off by the radium element, which is of therapeutic value. The beta rays, or burning rays, are harmful and must be eliminated by proper screening. The alpha rays are weak and are of no significance. Radium does not remove a cancerous growth by destruction of the entire part affected, as is accomplished by surgery or cauterization, but the gamma rays have a direct selective action on the cancer cells, destroying them without injuring the normal cells at the site of the neoplasm. This is demonstrated in healed cases of carcinoma of the cervix, where the normal shape of that organ may be restored without trace of the site of the growth.

Another action of radium is to cause proliferation of the connective tissue. The connective tissue contracts, with resultant obliteration in a great degree of the blood and lymph supply, producing the contracted, pale-looking cervix and funnel-shaped vaginal vault noted in ideally healed cases.

If the dosage suitable for a certain case is used, the cancer cells, but *not* the normal tissues, will be destroyed, owing to the selective action of the gamma rays on the carcinoma, and the greater resistance or toleration of the normal tissues. If much larger doses of radium than is required to destroy the cancer cells are given, the normal structures will also be destroyed, thus producing extensive necrosis with its resulting septic absorption, hemorrhages, and injury of adjacent viscera, with, perhaps, the production of fistulas. These unfortunate results of overradiation with this powerful element are commonly attributed to the extension of the carcinoma, or, frequently, the action of the radium is blamed and, consequently, condemned as of no value. We must also

The last menstrual period (Sept. 10, 1938) was followed by mild lower abdominal pain and slight spotting on October 10. No other symptoms developed. Pelvic examination on November 4 showed a two months' pregnant uterus. The Gräfenburg ring could be palpated through the anterior uterine wall at the level of the internal os. X-rays showed the ring clearly. The patient was admitted to the hospital, and, under nitrous oxide anesthesia, the cervix was gently dilated, the ring grasped with hemostats and removed (Fig. 1). Large doses of pantopon

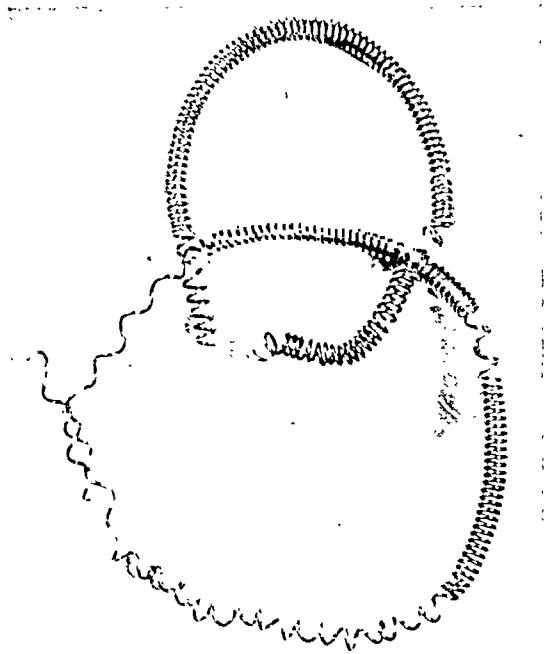


Fig. 1.

were given, and, after four uneventful days, the patient was discharged from the hospital. The remainder of her pregnancy was uncomplicated, and she delivered a healthy eight-pound baby spontaneously on June 5, 1939. The puerperium was afebrile and uneventful; mother and baby were in good health at last report (February, 1940).

807 SPRUCE STREET

Vignes, H.: The Nicolas-Favre Disease in Gynecology and Obstetrics, *Rev. franç. de gynéc. et d'obst.* 34: 215, 1939.

The pathogenic agent responsible for the Nicolas-Favre disease is a specific filtrable virus which is lymphotropic. The patient exhibits a chronic vulvar ulceration with hypertrophy or perigenital masses with or without a rectal stricture or an obstruction during labor. The cases with vulvar manifestations are usually seen in clinics for venereal diseases. Because of the marked induration, these lesions produce formidable obstructions to normal delivery. In some cases these lesions are associated with inexplicable peritonitis.

Vignes emphasizes the strikingly large number of fetal deaths in these patients. He mentions a case reported in the literature where not only the mother but also the baby soon after birth had a positive Frei test.

J. P. GREENHILL.

pelvic floor, and in 8 cases of plastic operation on the vaginal walls. There were 2 cases of hemorrhage in which the cause was undetermined.

Weintraub of Brooklyn, in a recent report, found the frequency of uterine hemorrhage in 4,421 gynecologic cases other than pregnancy, to be 738 or 16.6 per cent. The most common single cause was fibromyomas, in 46 per cent. Endometrial hyperplasia occurred in 23.7 per cent, usually associated with follicular cysts of the ovary; 9.2 per cent were due to fibrosis uteri, 6.6 per cent to cervical or fundal polyps, and to malignancy in 3.7 per cent.

Floyd Keene, of Philadelphia, studied 782 cases of postmenopausal bleeding and found 60 per cent were due to malignancy; 78.4 per cent were associated with some form of neoplastic disease of the cervix, fundus, or adnexa, and 75.4 per cent of these were malignant. In the entire series, bleeding was of cervical origin in over one-half of the cases, and 56 per cent of these lesions were malignant; 40 per cent were fundal in origin, of which 61.5 per cent were malignant. In 38 cases no organic lesion could be found.

Howard Taylor, Jr., of New York, in a study of 406 cases of postmenopausal bleeding, and TeLinde of Johns Hopkins Hospital, in a study of 349 cases, found approximate percentages.

Postmenopausal bleeding, especially after a year, therefore, is always important, as, with a normal cervix, two-thirds of the cases are of malignant origin.

FUNCTIONAL HEMORRHAGE

Uterine hemorrhage may be regarded as functional only when no general or local lesion can be found, the bleeding symptoms in all being similar. Functional bleeding may occur during adolescence, the reproductive period, at the menopause, and later. The accepted theory is that it is due to a disturbance in the ovarian rhythm.

As the cyclic phase of the endometrium reflects the ovarian activity, a biopsy of the endometrium is essential as an index of the ovarian function in all cases of functional bleeding, and the most common finding is that of hyperplasia, frequently of the polypoid or Swiss cheese type.

The thyroid gland is an important factor in adolescence. Hyperthyroidism or hypothyroidism may be a factor in irregular bleeding, and the basal metabolic rate should be ascertained and the appropriate therapy employed.

Fatal functional bleeding has occurred in adolescence.

In functional bleeding in women of the childbearing age where hormone therapy has failed, curettage and intrauterine application of radium of from 300 to 400 mg. hours is indicated. We have found that 600 mg. hours is within the danger zone of castration.

Norris and Behney of Philadelphia, in 1,437 cases of benign hemorrhage, found that 750 cases were functional and 687 were myomas. Satisfactory results were obtained in 83 per cent by the use of intrauterine radium therapy; 3 per cent developed relapses ten years or more later. Carcinoma developed after irradiation in 1.09 per cent.

In functional bleeding at or after the menopause, the most satisfactory treatment is a diagnostic curettage to rule out possible malignant disease, and the intrauterine application of radium, 1,800 mg. hours being an average dosage to insure permanent stoppage of the bleeding. We believe this is preferable to ovarian radiation by the x-ray. Transfusion should be used in patients with a low hemoglobin.

remember that if too small an amount of radium is used, or for too short a time, we may fail to destroy all the cancerous tissue.

The elimination of the beta, or burning, rays, which cause extensive destruction of the normal tissue, depends upon the proper screening of the radium. Various metal containers of different thickness are used for this purpose, such as platinum, gold, silver, or brass, and damage of the bladder and rectum is avoided by "distance screening," that is, pushing them out of reach of the rays by overdistingding the vagina with gauze. If inadequate screening has been used, unnecessary necrosis will result.

Too frequently repeated radiations, especially if a heavy dosage for prolonged periods is employed, will result in the so-called "late reaction" of radium. Six months, or a year or more following the initial treatment, dense infiltration, pelvic pain, ulceration, and discharge may develop, which is likely to be attributed to a *recurrence* of the disease, when it is actually the result of an overirradiation of the tissues, with a resulting excess of connective tissue formation. This produces a slowly developing obliterative arteritis, and the devitalized structures ulcerate and become a ready prey to infection.

Radium also has an action on the ovaries, the follicular apparatus being very sensitive to the rays, so that it may be destroyed, with a resulting atrophy of the organ, inducing the menopause, as in castration. This action of radium may be used to control excessive uterine bleeding by retarding the ovarian function. It also has a local action in the endometrium, causing destruction of the glandular elements, with replacement of connective tissue. The castration effect on the ovaries naturally results in atrophic changes, to which may be attributed the shrinking, or even disappearance, of myomas. The element, either in the form of a salt or the emanation, may be used with equal results. Our work at the Woman's Hospital in New York has been done entirely with the salt in the form of radium barium sulphate.

Large quantities of radium are not advantageous for internal application. The curative penetration of the gamma rays, in amounts which may be safely used, is limited to about 3.5 cm. Necrosis of the tissues may be caused at the site of application by the gamma rays breaking up into secondary rays from the metallic screens and their action on striking the tissues. An attempt to limit the action of these secondary rays is made by using aluminum or pure rubber protection. It is of no avail to attempt to secure a deeper penetration in an effort to reach the parametrium by greatly increasing the amount of radium in the container, because the intensity of radiation is decreased inversely in proportion to the square of the distance, and the result would be a marked and unnecessary increase of the local damage without appreciable gain in penetration.

FREQUENCY AND ETIOLOGY OF BLEEDING

In the past ten years, 19,603 gynecologic patients were discharged from the Woman's Hospital in New York. Severe hemorrhage, as a predominant symptom, occurred in 371 cases, or nearly 2 per cent. It was present in 254 tubal pregnancies, as a complication in 4 cases of carcinoma of the fundus of the uterus, and in 53 cases of carcinoma of the cervix. Secondary hemorrhage as a postoperative complication occurred in 26 cases of amputation of the cervix, in 23 cases of cauterization or conization of the cervix, in 1 case of plastic operation on the

uterus and the corrosive action of the menstrual ferment trypsin, all favor rupture of the delicate superficial vessels on the surface of the submucous growth, and necrosis or trauma causes rupture, with resulting menorrhagia or metrorrhagia with clots. This is always of a venous type and may be controlled by packing. Bleeding from a fibroid uterus after the menopause is always to be considered of importance. It may be from a necrotic submucous growth, sarcoma or carcinoma.

Surgery is indicated in bleeding myomatous uteri, as a general rule. Myomectomy in the childbearing age, with removal of a submucous growth by vaginal hysterotomy, may be possible. If the myomatous invasion of the uterine musculature is too extensive, hysterectomy is indicated with conservation of the ovaries in young women.

Radiation is not suitable in the third or fourth decades for bleeding in the presence of myomas, as a sterilizing dose is necessary to produce the desired result. An inadequate nonsterilizing dose will give temporary relief of the bleeding, but the myomas will develop further. Radiation is excellent in the fifth decade for abnormal bleeding with associated small intramural growths. A sterilizing dose must be given so as to destroy the function of the ovaries. Radium is preferable to x-ray therapy in my experience in such cases. Radium is of no use in the treatment of postclimacteric fibroids without bleeding. If the growths produce pressure symptoms, hysterectomy is necessary.

Adenomyosis is a nonneoplastic disease, but is due to an invasion of endometrial glands into the uterine muscle tissue with resulting hypertrophy. Sampson's theory of endometriosis may account for the invasion of the musculature of gland elements. Abnormal bleeding is the most important symptom, usually with a profuse menorrhagia and a symmetrically enlarged uterus without intermenstrual flow. Radiation therapy is of little benefit in this type of disease, and its failure to relieve the bleeding may be of diagnostic value. Surgery is indicated.

Generally speaking, benign ovarian neoplasms do not cause bleeding, and until their size is demonstrable or complications set in, they are frequently not discovered. Cystic degeneration of the ovaries may develop prolonged menstruation or "spotting" due to the imperfect formation of the corpus luteum, especially if there is formation of a corpus luteum cyst. Simple follicular cysts frequently cause no menstrual irregularity. Menstrual disorders are noted in about only 12 per cent of dermoid cysts and pseudomucinous cystadenomas. The granulosa cell type of tumor, however, is frequently associated with bleeding.

These ovarian neoplasms are all best treated by surgery and not by radiation therapy. In patients beyond 40 years of age with fibroid uteri, radium therapy may be employed successfully only where the physical and symptomatic conditions present are suitable. Each case must be given individual consideration.

It is well to remember that 28 per cent of all women over thirty-five years of age have fibroids in some degree, and many are without symptoms throughout life. These cases should, of course, be watched, but without symptoms treatment may not be essential. When bleeding occurs as a symptom, about one-third may be treated successfully with radium. The limitations, however, are definite. Radium is not suitable for women who desire the preservation of the menstrual function and possible future pregnancy.

If, in postmenopausal bleeding, with a slightly enlarged uterus and ovary, the biopsy reveals a hyperplasia of the endometrium, a granulosal cell tumor should be suspected.

NONMALIGNANT DISEASES

The benign conditions which may be treated by radium therapy are derangements of the physiology of the uterus, as a result of ovarian or pituitary dysfunction, or the menopause, and the symptoms produced by benign neoplasms. The outstanding objective symptoms of these benign or malignant conditions are uterine bleeding, either in excess at the menstrual period, or in irregular and too frequent periods, "spotting" or in prolongation of the menopause. It will be of value, therefore, to consider uterine hemorrhages in this connection.

Uterine bleeding, other than the normal physiologic loss of blood during menstruation, is probably one of the most frequent conditions that the general practitioner, as well as the gynecologist, has to contend with, and a correct diagnosis as to the cause may be of vital importance as to whether it is of benign or malignant origin.

The causes of nonmalignant hemorrhages may be classified as follows:

1. Functional hemorrhages, as a result of endocrine dysfunction and imbalance, occurring at puberty, during the childbearing period, and at the menopause where there is no demonstrable lesion.
2. Hemorrhages associated with neoplastic diseases, including cervical and corporeal polyps, myomas, adenomyosis, and ovarian tumors.
3. Hemorrhages associated with inflammatory diseases, as salpingitis, oophoritis, and tuberculosis.
4. Bleeding from retained gestational products after abortion or full-term delivery.
5. Intra-abdominal hemorrhage, as a result of ectopic pregnancy, endometriosis and ruptured ovarian cysts and myomas.
6. Uterine bleeding from miscellaneous causes, such as cervicitis with erosion, subinvolution, hemophilia, hypertension, and postoperative hemorrhage.

NEOPLASTIC DISEASES

Cervical and fundal submucous polyps are prone to hemorrhage of a continuous "spotting" type, especially after coitus, douche or exercise, with menorrhagia at the menstrual period, and there is usually a polypoid type of endometrial hyperplasia present. The treatment is surgical.

Cervical or fundal submucous myomas are prone to severe and dangerous bleeding, probably as a result of necrosis and ulceration. It is the consensus of opinion that myomas which do not invade or encroach upon the endometrium are not the cause of uterine bleeding. There is a prevalent conception that abnormal bleeding is a specific characteristic of fibroids entirely distinct from hemorrhage from nonmyomatous uteri. As Graves of Boston has emphasized, the processes that lead to bleeding are hormonal and not dependent on the myomatous growth itself. The bleeding, then, in nonmyomatous and myomatous uteri is identical in origin, that is, hormonal.

There is no bleeding or change in the endometrium in fibroid uteri unless there are cystic changes and absence or defect in the corpus luteum of the ovaries, the exception to the above being in the submucous myomas. In such cases there is an abnormal vascularity of the growth, and the area of the uterine cavity is increased. The contractions of the

promptly; perhaps one subsequent period may occur. The growth will show a gradual shrinkage during a period of ten to twelve months.

Radium should only be used in women under 40 years of age, when serious systemic disease contraindicates a major surgical procedure.

In myopathic bleeding at the menopause, with frequent excess and prolongation of that period, permanent sterilization with radium is an ideal and simple procedure. It should always be preceded with a diagnostic curettage at the time of the application. The radium should be applied in tandem to the corpus, and the usual dosage is from 1,200 to 1,800 mg. hours, depending upon the size and thickness of the uterus.

In myopathic bleeding in the childbearing age, temporary sterilization with radium may be employed. From 300 to 400 mg. hours is the usual dosage which may result in a temporary amenorrhea for several months. A second application may be required later, but in my experience 600 mg. hours is near the danger zone of permanent sterilization.

In severe intractable cases of dysmenorrhea in young girls, temporary sterilization may be of some avail, but permanent sterilization is unwise because of the menopausal changes and symptoms which will ensue. Hysterectomy, with conservation of the ovaries, would be a much more satisfactory and justifiable procedure.

In endometriosis, a permanent sterilization would be necessary to effect a cure in most cases, and as this usually occurs in young women, surgery would be the method of choice, as some conservation of ovarian tissue may be possible.

Temporary sterilization with radium, however, will relieve symptoms in some cases with involvement of the rectovaginal septum. Temporary sterilization with radium in the childbearing age, according to Douglas Murphy and others, may possibly lead to developmental defects in subsequent offspring, appearing in the third or later generations.

Without doubt radiation *after* fertilization of the ovum in the earlier months of pregnancy will produce marked defects in the progeny. Therefore, radiation should never be done in the presence of pregnancy, except in cases of carcinoma.

MALIGNANT DISEASES

While cancer is a disease that attacks all parts of the body, about 25 per cent of female deaths from cancer are due to carcinoma of the uterus, and the average duration of life is about twenty to twenty-four months without treatment.

As cancer of the uterus is a type of the disease which every general practitioner encounters in his practice, it is largely to him that we must look for the early recognition of the disease and the education of his patients to the importance of promptly seeking a diagnosis on the appearance of suspicious symptoms.

We must appreciate that the disease originating in the cervix and that arising in the fundus must be considered separately, as the clinical course and the results of treatment are quite different in each instance.

CANCER OF THE CERVIX

Cancer of the cervix, by reason of the anatomic conditions, is by far the most dangerous form and the most difficult to cure, and is also the most frequent. At the outset we must admit that the results of the treatment of cancer of the cervix are far from satisfactory, but, at the

Indications and contraindications for radium therapy in uterine fibroids:

The size of the growth must not be over that of a three or three and one-half months' gestation.

The growth must be fairly symmetrical or globular in shape.

The most suitable cases are those with intramural fibroids.

Subperitoneal or pedunculated growths outside the range of the rays are not influenced by the radium.

Submucous fibroids are a contraindication to radium on account of the danger of infection. Rapidly growing growths suggest sarcoma or progressing degenerative changes and are not suitable.

It is essential that the adnexa be entirely free from pathology.

Fibroids showing degenerative changes, as indicated by infection (temperature and tenderness), or anemia out of proportion to the blood loss, are not suitable for radium therapy.

TECHNIQUE OF APPLICATION

It is our opinion that anesthesia in some form should be employed in all cases in which radium is employed. This not only prevents suffering, but allows a thorough examination and exposure to insure a correct diagnosis, enables the operator to make an accurate application and fixation of the element in the situation desired, and to place adequate screening for the protection of the adjacent organs. Likewise, a diagnostic curettage should always be done at the time of the application in all suspicious benign cases, as not infrequently an adenocarcinoma of the fundus may be discovered which will, of course, alter the conduct of the case. Gas-oxygen anesthesia is sufficient, and in many cases a half dosage of spinal anesthesia is very satisfactory.

In the treatment of fibroids the radium should be so distributed in the container, as to contact as much of the endometrium of the corpus uteri as is possible, covering the area from fundus to internal os.

It is most important that the container should be anchored in its position, as the natural contractions of the uterus to expel a foreign body are often the cause of an unsatisfactory result or a radium burn of the vagina.

It is our custom to always test the presence of the radium in the applicator with an electroscope at the time of the insertion. This is a wise precaution.

The amount of radium element used in the treatment of fibroids is usually two tubes of 50 mg. each, placed in tandem formation in a container giving an equivalent of a milligram of platinum screening, with a pure rubber or aluminum outer filter to eliminate the secondary rays. The dosage for myomas averages from 1,200 to 2,400 mg. hours, depending upon the size of the uterus and the thickness of the uterine walls.

Great importance is attached to the insurance of the maximum of distance screening by distending the balloon-shaped vagina to the utmost with firm gauze packing, in order to displace the adjacent bladder and rectum as far away as possible from the effect of the rays. This naturally interferes with the patient's ability to void, so it is well to insert an indwelling Pezzer catheter, not only to avoid repeated and sometimes difficult catheterizations, but also to keep the bladder collapsed, and the posterior bladder wall is thus kept away from the danger zone of radiation through the anterior uterine fundus. One application only is best in these cases. The hemorrhage will be checked

use of radium by those not qualified. The renting of radium from commercial agencies is, of course, perfectly justifiable, but the knowledge and judgment as to how and when to use it can only be accomplished by careful study and personal experience and observation in radiologic clinics. I cannot do better than to quote Regaud's recent warning: "It is necessary to have much experience to obtain from this method of treatment all the good that it may give without the evil that it may do."

Two main histologic types of cervical carcinoma are recognized—the epidermoid carcinoma and the adenocarcinoma. The epidermoid carcinoma, which is much the most frequent, is divided into three classes, according to the differentiation of the type of cell. The epidermoid group is the most common form, and the cell types are designated as the squamous or spinal cell, which is the most mature or "ripe" cell, the transitional or plexiform "midripe" cell, and the anaplastic spindle, "unripe" cell.

The adenocarcinoma is chiefly recognized by its glandular form of growth.

The importance of recognizing these various types of cancer cells will be appreciated when we understand that they respond differently to irradiation. The "Law of Bergonie and Tribondeau" states that "Immature cells and cells in an active state of division are more sensitive to irradiation than are cells which have acquired their fixed adult morphologic and physiologic character." The squamous spinal, or mature, cell is much the more radioresistant and, at the same time, it is more slowly growing and the least malignant type, while the embryonic anaplastic "unripe" spindle cell is the least radioresistant, but the most rapidly growing and most malignant type. The transitional or "midripe" cell is midway between these two extremes in responding to irradiation. Adenocarcinoma of the cervix is, fortunately, much less frequent (our ratio is about 13 to 1), as it is very radioresistant and more difficult to cure.

The ability to make a prognosis as to the probability of obtaining a cure by studying the type of cell is open to debate and is not uniformly accepted, as it is evident that many other factors must be taken into consideration, notably the extent of the disease and the physical resistance of the patient; also that the ordinary biopsy does not permit a study of the complete specimen which may show considerable variation in the type of cell differentiation in various regions.

TOXEMIA

The physical condition of the patient may have an important bearing on the reaction produced by the radiotherapy. Many of these patients are anemic and cachectic, and suffering from toxemia as a result of the absorption of necrotic carcinomatous tissue. Frequently, they are septic due to a local infection of the ulcerated areas. The immediate result of the radiotherapy in such cases is to produce a severe reaction on account of the absorption of the autolytic and toxic protein substances which have been liberated by the destruction of the cancer cells.

This "radiation sickness" is naturally more severe in those patients who are already toxic and anemic, and this systemic condition prevents the defense mechanism from promoting the prompt healing of tissues. The effect of the radium is to produce a leucopenia, and the patient's

same time, we must appreciate that there has been a considerable gain in the percentages of cures and palliations as a result of modern methods. We have a choice of treatment in the operable cases of surgery or radiotherapy, but if we use surgery we must employ the radical Wertheim technique.

The difference between the ordinary panhysterectomy and the Wertheim operation may be best appreciated when likened to a simple mastectomy, as compared to the modern radical removal of the breast with the pectoralis muscles, and the thorough cleaning out of the axilla of the lymphatic glands. A simple mastectomy for cancer of the breast would not be considered justifiable from the surgical standpoint today, yet it is known that many women with cancer of the cervix are being subjected to an ordinary hysterectomy instead of the radical operation, due to the fact that the average general surgeon is not competent, owing to the lack of experience and failure to develop the necessary skill, or he fails to appreciate what the technique of the radical operation should be.

One of the outstanding surgeons in this particular field today is Victor Bonney of London, and I would commend his Hunterian Lecture on the "Surgical Treatment of Carcinoma of the Cervix" to those who wish to obtain a proper appreciation of the technique and the difficulties of this formidable operation.

There is no difference of opinion as to what is the best treatment at our disposal for the inoperable class. Radiotherapy is admittedly our most valuable palliative measure, definitely prolonging life and, in a small percentage of cases, approximately 12 per cent, accomplishing a cure.

Today, owing to the technical difficulties and the prolonged hospitalization and suffering, and to the high primary mortality rate, 8 to 17 per cent, with no gain in so-called cures, surgery has largely been replaced by radiation therapy in cancer of the cervix, with its primary mortality of less than 2 per cent, and an even greater salvage.

The technique of the application of the radium in these cases seems so simple that it is difficult to impress upon the casual observer that success and safety depends upon the careful study of the location and extent of the disease, of the type of cell and the degree of its maturity, of the general physical state of the patient as to age, blood condition and toxemia, of the careful preoperative preparation of the patient, of the amount of radium used and its distribution in appropriate containers, on the proper employment of screening to cut out the burning rays, on the placing and maintaining of the radium in situ where it will destroy the cancer and yet not damage adjacent viscera, on the duration of the application, and the time and dosage of reradiations and deep x-ray therapy, and, finally, on a careful frequent follow-up. A personal experience in studying the action of radium on this disease over considerable periods of time is essential before one can become competent to treat properly cancer of the uterus with radiotherapy.

This statement may be made in spite of the assurances given the practitioner in the alluring advertisements in the medical press, that it is so simple that all he has to do is to send a description of the case and the radium with full directions will be forwarded. Correspondence courses in radiotherapy are dangerous, and I wish to sound a warning as to the serious harm that may result from the indiscriminate application of radium by inexperienced hands. I have seen a number of instances of grave permanent damage through the careless and ignorant

developing fistulas in 8.7 per cent, severe hemorrhage in 12.9 per cent, rectal disorders in 6.1 per cent, bladder and urethral symptoms in 9.8 per cent, the upper urinary tract was involved in 5.6 per cent, upper gastrointestinal symptoms in 2 per cent, blood and lymphatic obstruction in 4.2 per cent, and nervous disorders, pain, etc., in 3.7 per cent.

Upper urinary tract disease, which occurred in 39 of the 688 cases, was usually a late development and was due generally to obstruction of the ureter, with resulting infection, hydronephrosis and pyonephrosis, or destruction of the kidney. The ureteral obstruction was demonstrated by catheterization in these cases and was usually 4 cm. from the orifice. The action of radium, which produces a proliferation of the connective tissues with subsequent contraction, is responsible for the complication in many cases, due to the proximity of the ureters to the sides of the cervix as they pass through the base of the broad ligaments, although the invasion of the carcinoma into the same region is a frequent cause. Therefore, all patients should have a complete urologic examination before being given radiation therapy in order to evaluate properly damage by radium.

In the earlier cases, hopeless cases, and cases lost in the follow-up examinations, complications were not always accurately recorded. There are also many duplications, as one complication precedes or is an early stage of another. This gives us an index of the price these patients had to pay for radium therapy. Except for hemorrhage, each of these complications occurred in less than 10 per cent of the cases. The majority of complications are less frequent in the patients destined to survive, and many are of a transitory nature.

All of the untreated patients die of the disease, and the complications of the various organs involved are, of course, due to the carcinoma. In the treated patients that die the complications often appear shortly before death, and in many they are also due to the disease itself and not to the radiotherapy. The development of complications, then, we must always regard as an unfavorable sign, as in many cases it is an indication of a probable extension of the carcinoma. However, we have been agreeably surprised in some instances to see a patient whom we had considered in a hopeless condition report to the follow-up clinic some months later restored to health, with an arrest of the disease. These patients undoubtedly were suffering from late radium reactions and not from the progress of the carcinoma. We have learned, therefore, to reserve judgment on the outcome of these hopeless cases.

The essential features of the technique employed at the Woman's Hospital in carcinoma of the cervix are as follows:

The classification of the extent of the disease by both the Schmitz and the League of Nations systems, and the recording of the same on life-sized charts.

The preliminary building-up of the patient's resistance in cachectic cases by a blood transfusion.

Anesthesia of some type is necessary for accurate diagnosis and biopsy, and for the correct application of the radium.

A biopsy is taken with the radio-knife.

An initial dosage of 3,600 to 4,200 mg. hours of radium is given, depending upon the extent and size of the cancerous growth. One hundred milligrams are placed intracervically, with the equivalent of 1 mm. of platinum screening, and in the periphery at the junction of the cervix with the vaginal fornices 4 or 6 platinum needles (0.5 mm.), containing $12\frac{1}{2}$ to 13 mg. each, are inserted for twenty-four hours. Ten to twelve days later a second application of 75 mg. of radium in 6

resistance needs to be fortified to combat this condition. Hence, the value of blood transfusions is to enable the patient to "weather the storm" and make a smoother recovery.

External Radiation.—As the beneficial action of the gamma rays of radium is limited to a range of 3 to 4 cm., it is apparent that if the cancer has spread beyond this distance, the local radium application will not be sufficient to eliminate the disease. Bonney found 43 per cent of gland involvement in his operative cases, and it is to this that he attributes the superiority of surgery.

External radiotherapy, by means of the high voltage deep x-ray apparatus, or by using a radium pack, or "bomb" at a distance, is necessary to attack the disease when beyond the reach of the internal radiation. The use of radium at a distance requires a large amount of radium, 2 to 4 Gm., so that the method is not available except in a few institutions.

Nearly all radiologists are of the opinion that the combined treatment is necessary to obtain the greatest benefit.

The Limitations of Radiotherapy.—To find the balance between the dosage necessary to destroy completely the neoplastic cells, and at the same time keep within the minimum dosage which will destroy normal tissues, is the problem that the radiologist must meet. It is obvious that the conditions in each case may vary greatly. The type of cell, the physical characteristics of the growth, the size and condition of the organs affected, and the constitutional state of the patient are all factors which must be carefully weighed in planning the dosage and technique best suited for the case under consideration.

Regaud has pointed out that radium is not a cure for every case of cancer. It is with the epidermoid type that the best results have been obtained. The adenocarcinomatous group are more difficult to cure. In the cases where the parametria are involved, the proportion of five-year cures is small, although the palliative results, even in many advanced cases, are of great value in prolonging life and reducing suffering.

THE COMPLICATIONS OF RADIOTHERAPY

There is a general impression that the convalescent period with radium is without the same suffering and is much shorter than with surgery. This impression, however, is open to question, and a careful comparative study of postirradiation convalescence with convalescence from radical surgery should be made to evaluate properly radiotherapy. In other words, "What price radium?"

After an experience of more than fifteen years in the use of radium in carcinoma of the uterus, we believe that a ten-year postirradiation observation period gives us a more accurate evaluation of the curability of cancer by radiation than the usual five-year standard. An estimation of postirradiation mortality and morbidity is naturally confused and complicated by the ravages of the disease itself.

As three-fourths of all cases seen do not survive the five-year period, it is reasonable to assume that the cancer is responsible for the mortality and much of the morbidity rather than the irradiation.

An approximate indication of the incidence of complications in a series of 688 cancer cases treated with radium, seen during three five-year periods, shows that pyometra was observed in 7.9 per cent, peritonitis and sepsis in 1.5 per cent, intestinal obstruction in 3.6 per cent, patients

sponsibility is assumed in not giving the patient the full benefit of our present-day knowledge.

Radium is a two-edged weapon, and a proper training in its use is just as essential as in surgery.

It is well to emphasize the fact that the safe employment of radium requires experienced piloting, as we are sailing in tortuous channels with rocks on either side. It may be likened to Vergil's lines:

"There on the right her dogs foul Scylla hides,
Charybdis roaring on the left presides."

101 EAST 80TH STREET

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 12, 1940

The following papers were presented:

Endometrium-Like Mucosa Lining the Fallopian Tube. Dr. Andrew A. Marchetti. (By invitation.) (For original article, see page 69.)

Management of the Occipitoposterior and Retraction Ring Dystocias in Primiparas. Dr. George G. Cochran, Jr. (By invitation.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF FEBRUARY 1, 1940

The following paper was presented:

Toxemias of Pregnancy. Dr. M. Pierce Rucker, Richmond, Va. (By invitation.)

MEETING OF MARCH 7, 1940

The following papers and case reports were presented:

The Suppression of Lactation by Stilbestrol. Dr. C. W. Mucklé. (For original article, see page 133.)

Stilbestrol in the Treatment of Menopausal Symptoms. Drs. F. L. Payne and C. W. Mucklé. (For original article, see page 135.)

Chronic Nephritis and Pregnancy Fatalities in Philadelphia. Dr. N. F. Paxson.

Successive, Coexistent Tubal Pregnancies. Drs. C. A. Behney and W. J. Hanes. (For original article, see page 155.)

Removal of a Graefenburg Ring Without Interruption of Pregnancy. Drs. R. A. Kimbrough and P. Tompkins. (For original article, see page 156.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 16, 1940

The following papers were presented:

The Treatment of Oliguria and Anuria. Drs. W. J. Dieckmann and S. Kramer. (For original article, see page 61.)

Congenital Goiter. Drs. A. H. Parmelee, Edward Allen, Irving F. Stein, and Henry Buxbaum. (For original article, see page 145.)

Epidemic Infectious Diarrhea of the Newborn Infant. Drs. R. S. Cron, H. W. Shutter, and A. H. Lahmann. (For original article, see page 88.)

platinum needles in two silver boxes in a spring colpostat is made to the vaginal vault. Each box approximates the lateral fornices of the vagina at the base of the broad ligaments for twenty-four hours. Thus the total radium therapy averages from 5,400 to 6,000 mg. hours.

In cases where there is an exuberant cauliflower mass protruding into the vagina, it is removed with the high frequency knife before applying the radium.

We stress the importance of distance screening by distending the vagina with gauze to its capacity to keep the bladder and rectum as far away as possible from the radium rays, and we use a self-retaining catheter to keep the bladder collapsed during the radium application. We believe that anchoring the radium tube in the uterus is an important detail.

Potassium permanganate douches and an elevated posture to promote drainage and separation of any slough are begun at once.

Adjuvant high-voltage roentgen therapy has been employed since 1930, and since 1933, the fractional method of Coutard has been used whenever it is possible to have continued cooperation of the patient for the necessary length of time. In certain cases of advanced carcinoma, we precede the application of radium with roentgen therapy, according to Healy's plan. Two hundred roentgen units are given to one anterior and one posterior portal daily until all portals have received 2,000 to 2,400 roentgen units each.

The outstanding feature of our method, however, is the frequent follow-up inspection made by the surgeon himself throughout the five-year period, if at all possible. During the first three years a monthly inspection is made, and after that the patient is seen every two or three months. If the follow-up examination discloses evidence of a beginning recurrence in the vaginal walls or fornices, a further irradiation is given in time to check the recurrence in its incipency.

In carcinoma of the fundus uteri, we believe that panhysterectomy should be resorted to wherever possible and that the ideal procedure is the combined method of diagnostic curettage with immediate insertion of radium in the cavity, the radium to remain for from 2,400 to 3,600 mg. hours, followed by a panhysterectomy and salpingo-oophorectomy within four to six weeks, and on recovery a course of roentgen therapy, preferably by the Coutard technique.

RESULTS

The comparison of statistical results in the treatment by radiotherapy of carcinoma of the cervix in the different clinics of the world shows an improvement over the earlier reports. The report published by the League of Nations in 1938 shows the results of the 1931 series from seven clinics in Europe, and two from the United States, the Memorial and the Woman's Hospital clinics representing this country. A total of 5,672 patients were treated, with a relative 5-year cure rate of 26.3 per cent, and of the 607 Stage I cases, the relative cure rate was 55.2 per cent.

A survey of the six statistical reports of our results shows an improvement in the relative five-year cure rates we have obtained as follows: 1925, 23.6 per cent; 1928, 23.1 per cent; 1930, 25.5 per cent; 1932, 24.8 per cent; 1934, 25.28 per cent, and 1937, 28.5 per cent.

CONCLUSIONS

The safe and efficient use of radium requires judgment and experience.

A thorough understanding of its action and an appreciation of the complexities of its application are necessary, otherwise a grave re-

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Myoma and Endometrioma

DaCosta, C. C.: Myoma of the Vagina, *Rev. de gynec. e d'Obst.* 1: 257, 1939.

The author states that myoma of the vagina is very rare. He was able to find only one case in the literature, reported by Caper in 1935. The article deals with the differential diagnosis between cysts and tumors of the Bartholin gland, and the author describes in detail a case of myoma of the vagina, operated on by him. Histologic examination reveals all the characteristics of a myoma. The article closes with several theories on the etiology of vaginal myoma and its prognosis.

MARIO A. CASTALLO

Kanter, A. E., and Klawans, A. H.: Fibroids of the Uterus, *Illinois M. J.* 76: 459, 1939.

The authors have drawn their conclusions from 300 consecutive patients operated upon at the Cook County Hospital. They find that parity has no demonstrable relation to fibroids, although sterility may be a direct result of the tumor. They also find that the textbook symptoms ascribed to fibroids of the uterus, namely, menorrhagia, dysmenorrhea, leucorrhea, and bladder symptoms, are determined entirely by the location of the growth and not due to the fibroid per se. In conclusion, the authors make a plea against additional elective surgery, such as appendectomy or perineorrhaphy, in conjunction with hysterectomy, as these elective procedures apparently doubled the mortality figures in their series of cases.

EUGENE S. AUER

Portes, L.: Note on the Connection Between Uterine Fibromas and Hyperfolliculinemia, *Bull. Soc. d'obst. et de gynéc.* 27: 275, 1938.

The author reports a case in which he found an excessive amount of estrin in the blood, coincident with rapid growth of a fibroid uterus. This finding supports the contention of Seitz, Moench, and Witherspoon that uterine fibroids are associated with an increase in amount of circulating estrin. The arguments in favor of this theory are as follows: (1) Uterine fibroids appear only after puberty and disappear after the menopause, and this agrees with the period of estrin activity of the ovary. (2) The suppression of ovarian estrogenic activity by radiation results in the diminution or disappearance of fibroids. (3) Uterine fibroids sometimes grow rapidly during pregnancy, at which time there is a very important increase in the amount of circulating estrin. Hence, it should be possible to treat fibroids with endocrines at least at the beginning of their growth and reserve operation for mechanical complications of the tumor or for tumors which undergo degeneration.

J. P. GREENHILL

Langlois: A New Treatment of Uterine Fibroids, *Bull. Soc. d'obst. et de gynéc.* 27: 179, 1938.

In the treatment of uterine fibroids, Langlois has been using halogen salts of magnesium. Hypodermic injections are administered every day for four to six months. Then the treatment is stopped for one or two months and again resumed. Improvement is noticed after the first course of treatment. The author reports four cases where the bloody discharge disappeared and the fibroid masses slowly regressed.

J. P. GREENHILL

MEETING OF MARCH 15, 1940

The following papers were presented:

A Study of 1200 Cases of Hysterectomy. Dr. Philip H. Smith. (For original article, see page 118.)

Prolapse of the Umbilical Cord. Drs. W. F. Mengert and F. H. Longwell. (For original article, see page 79.)

An Acute Crisis of Suprarenal Insufficiency Complicating Pregnancy. Drs. C. E. Galloway, D. C. Sutton and John Ashworth. (For original article, see page 148.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 2, 1940

The following papers were presented:

Syphilis and Pregnancy. Dr. William T. Daily.

Chorioepithelioma. Dr. C. W. Mueller, H. J. Greene and J. Klein.

Uterine Bleeding in the Last Trimester of Pregnancy. Dr. J. T. Wallace. (For original article, see page 128.)

Renal Insufficiency Following Transfusion of Compatible Blood. Dr. H. H. Brainard. (For original article, see page 142.)

MEETING OF MARCH 1, 1940

The following paper was presented:

Relationship of the Thyroid and Adrenal Glands to the Toxemias of Pregnancy. Dr. E. C. Hughes, Syracuse, N. Y. (By invitation.) (For original article, see page 48.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL
SOCIETY*MEETING OF FEBRUARY 5, 1940*

The following papers were presented:

Four Unusual Cases of Ectopic Pregnancy. Dr. David B. Ludwig.

The Misleading History in Four Cases of Ectopic Pregnancy. Dr. S. A. Rubin.

Ovarian Cysts Complicating Pregnancy. Dr. R. Charles Nucci.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF FEBRUARY 20, 1940

The following paper was presented:

Surgical Complications of Pregnancy. Drs. J. A. Smith and M. K. Bartlett.

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND
GYNECOLOGISTS*MEETING OF FEBRUARY 9 AND 10, 1940*

The following papers were presented:

Use of Radium in the Menopausal Type of Uterine Hemorrhage. Dr. G. R. Holden.

The Third Stage of Labor With a Description of a New Method of Expression of the Placenta. Dr. C. J. Andrews.

The Post-Partum Bladder. Dr. J. R. Perdue.

Indictment of Diethylstilbestrol. Drs. R. B. Greenblatt, R. Torpin and W. R. Brown.

Nutrition Study in Pregnancy. Dr. Philip F. Williams, Bernard Hark, and Florence G. Fralin. (For original article, see page 1.)

Menorrhagia and epimenorrhagia are present in about 40 per cent of the cases and may be extremely severe, especially if the uterus is involved. The excessive or irregular blood loss may be partly due to the presence of associated fibroids, but is mainly a reflection of disturbed ovarian function; indeed in some cases the uterine endometrium has the thick, polypoid and hyperplastic appearance characteristic of metropathia hemorrhagica.

Dyspareunia may cause the patient much discomfort and mental distress and is met with in its most severe form when the endometriosis involves the structures behind the posterior vaginal fornix.

On the other hand, severe pelvic endometriosis may be quite painless, but this is exceptional, and the pain, particularly during menstruation, is frequently so severe that the patient is willing to undergo any treatment, however radical, to obtain relief from it.

Endometriosis has an adverse influence on fertility, and in this connection it is important to consider the age incidence of the disease.

Excluding cases with associated fibroids, single women and women married less than three years, 40 per cent of the patients were sterile, 32 per cent had not been pregnant for at least ten years and 23 per cent for at least five years.

Finally there is the question of treatment. When the lesions are extensive this must be radical and either surgical or radiologic. The author's preference is for surgery, and in severe cases he generally performs a hysterectomy with removal of both appendages. It is unnecessary and in fact dangerous to dissect out growths from the bowel wall, as there is ample evidence that these will retrogress if both ovaries are removed.

In less severe cases, particularly in young women, treatment should if possible be conservative, but it must be realized that this may afford only temporary relief and have to be followed later by more radical measures.

It is unfortunate that so many radical operations appear to be necessary, but one must remember that to be truly successful, conservative treatment should not only conserve function but also cure the patient. Many keen advocates of conservative surgery are likely to forget this in their anxiety to preserve the reproductive function.

In the meantime it should be possible to reduce the incidence of external endometriosis by treating such conditions as subinvolution, backward displacements of the uterus, and uterine fibroids which may predispose to retrograde menstruation, and by carrying out certain intrauterine diagnostic and operative procedures at a time and in a manner least likely to drive fragments of endometrium into and through the Fallopian tubes.

J. P. GREENHILL

Heynemann, T.: Endometriosis, Zentralbl. f. Gynäk. 63: 1, 1939.

The diagnosis of Endometrioma is still difficult. The condition can be recognized easily if it is visible through a speculum, colposcope, or proctoscope. In cases of ovarian endometriosis, pelvic puncture may help if the findings are in agreement with the clinical symptoms. In cases of endometriosis of the rectovaginal septum, biopsy may be useful. Philipp mentioned that the administration of large doses of estrin and progesterin increases the size and sensitivity of endometrial masses.

The author followed up the patients who had been treated for endometriosis in his clinic from 1920 to 1937. Of 40 women operated upon for ovarian endometriosis, one died as a result of the operation. In 21 of the remaining 39 women, some healthy-looking ovarian tissue was left behind, in 15 of them a whole ovary, and in the other 6 only a piece of ovary. In not one of these 21 women was there a recurrence of the endometriosis. In 13 women the menstrual function was maintained but only one became pregnant. The frequency of sterility in cases of endometriosis is well known, even when the tubes are patent.

In 47 women tubal adenomyosis in the form of a salpingitis isthmica nodosa was found. In 11 of these (22 per cent) tubal pregnancies were encountered. One of these 47 women died of pulmonary embolism.

Kangas, Toivo: Submucous Myomas, Expecially with Regard to Their Operative Treatment, *Ann. Inst. Obst. et Gynec. Universitatis* 11: 89, 1939.

The author collected the cases of submucous myoma treated at the Women's University Clinic in Helsinki and at Engstrom's Clinic. Of the 383 cases, 164 were pedunculated myomas: 96 were expelled into the vagina, 51 into the cervical canal and 17 remained in the uterine cavity. The submucous type of myomas seemed to be comparatively frequent in multiparas and particularly during the last decade of the procreative age. Ten per cent of the submucous myomas evoked pathologic hemorrhages. Of the myomas expelled into the vagina 75 per cent caused metrorrhagial hemorrhages in 75 per cent of the cases. Treatment by rest in bed and opium stopped pain. Before operation, an attempt should be made to increase the hemoglobin to above 50 per cent. The conservative extirpation of submucous myomas with a thin pedicle is a fairly harmless interference. The mortality was 0 in 113 cases. In primary radical operations, there is always the danger of complications (parametritis, thrombophlebitis, etc.).

J. P. GREENHILL

Vanverts, J.: All Uterine Fibroids Need Not Be Operated Upon Routinely, *Gynécologie* 37: 385, 1938.

Contrary to many surgeons, the author believes that frequently uterine fibroids remain latent and permit their hosts to lead a perfectly normal life. The number of such tumors is not small. Since there is some danger in operating or in using radiation therapy, treatment should be advised only when serious accidents or disturbances arise which must be suppressed. Sometimes medical measures may be used to overcome the inconveniences of fibroids.

In cases where active treatment is deferred, the fibroids must be examined systematically, at least every six months. The patient must also be warned to notify her physician should any disturbance arise. Such routine examination should not cease at the menopause, because fibroids may grow or produce trouble after the change of life.

J. P. GREENHILL

Azevedo, Moura, and Dutra, Licinio H.: High Partial Hysterectomy for Uterine Fibroma, *Rev. de obstet. e ginec. de São Paulo* 4: 3, 1939.

The authors present a new technique utilizing a U incision for partial hysterectomy in uterine fibroma. The incision is made in such a manner as to remove the mid-portion of the uterus, leaving the adnexa on both sides attached to the uterus. The author then utilizes the remaining sides of what formerly was the uterine body to cover the defect made. The remaining portions of the uterus are united from side to side.

MARIO A. CASTALLO

Dougal, Daniel: Endometriosis as a Pathological and Clinical Problem, *Edinburgh M. J.* 45: 61, 1938.

For every 100 cases of uterine fibroids, there are 6 cases of internal and 25 cases of external endometriosis. The latter is met with as the principal lesion or as an important complication, in about 10 per cent of all abdominal operations performed on the female genital organs.

The influence of endometriosis on the patient's general health depends on the frequency and severity of the principal symptoms and on the extent of the surgical treatment necessary to deal with them.

Pain in the lower abdomen is an important symptom of both internal and external endometriosis and may occasionally be of great severity. Dysmenorrhea, however, is undoubtedly the most characteristic symptom, particularly if of recent origin or becoming increasingly severe, although it was present in only about 50 per cent of the author's cases.

Navratil, E.: Endometriosis of the Extremities, *Klin. Wchnschr.* 18: 905, 1939.

In 1936, the author had reported the first known incident of endometriosis in the muscles of the arm in a 25-year-old patient. The tumor was a date-sized fibrotic mass in the carpi radialis externi muscle. Histologic examination showed a typical endometriosis with chronic inflammatory reaction. Repeated gynecologic examinations during 1935 and 1936 revealed no evidence of adenomyosis uteri nor of intra-abdominal endometriosis. Her past history was likewise negative.

Since this first report, the patient had a definite increase in the duration of her menstrual periods with marked increase in blood loss and the development of protracted dysmenorrhea. Her menstrual period also changed from a regular 28-day cycle to one that varied between 28 and 36 days.

Since November, 1938, the patient complained of continued pain in the right lower quadrant and moderate fever. Examination of the arm at this time revealed no recurrence of the endometriosis. The patient was operated upon in December, 1938. Both ovaries showed cystic degeneration and a total hysterectomy, bilateral ovarian resection and appendectomy were done. Careful search of the peritoneal cavity revealed no evidence of intra-abdominal endometriosis. Histologic examination of the uterus showed typical adenomyosis uteri interna with marked invasion of the myometrium by endometrial glands. The resected portions of both ovaries and of the appendix showed no endometriosis.

Here then is a patient in whom endometriosis of the muscles of the arm developed three years before any evidence of adenomyosis of the uterus could be elicited. The author is of the opinion that the onset in all probability dates back to a therapeutic abortion which had been previously performed. The author concludes that such metastasis must occur by way of the blood stream, the transmission being similar to that of living decidual cells during pregnancy. It would seem impossible to trace endometriosis as here described through any form of lymphatic transmission.

RALPH A. REIS

Item

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 5, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, immediately prior to the 1941 meeting of the American Medical Association.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pennsylvania.

Candidates certified by the American Board of Obstetrics and Gynecology at the June, 1940, examinations held at Atlantic City, N. J.

HARLEY E. ANDERSON, Omaha, Neb.
KENNETH M. ARCHIBOLD, Albany, N. Y.
IRVING H. BECKWITH, White Plains,
N. Y.
KARL M. BEIERLEIN, Fort Wayne, Ind.
MAURICE O. BELSON, Boston, Mass.
MARION T. BENSON, JR., Atlanta, Ga.

SAMUEL G. BERKOW, Perth Amboy, N. J.
MELVYN BERLIND, Long Island, N. Y.
PHINEAS BERNSTEIN, New York, N. Y.
WILLIAM MCK. BICKERS, Richmond, Va.
MARION E. BLACK, Cleveland, Ohio.
JOHN N. BORBONUS, Johnstown, Pa.
KENNETH B. BOYD, Baltimore, Md.

In cases of endometriosis where operation is contraindicated, roentgen ray therapy should be carried out. This will check bleeding and dysmenorrhea. During operation for endometriosis, healthy ovarian tissue should not be removed, especially if the tubes are patent. In cases of retrocervical endometriosis, the cervix should be removed but not the involved portion of intestine.

Not all cases of endometriosis require treatment. Only those which grow and produce symptoms should be treated. It has been shown that definitely proved endometriosis may not grow during a period of many years, even if ovarian tissue is left behind. This may occur even if one or both entire ovaries are left.

J. P. GREENHILL

Henderson, D. N.: Pelvic Endometriosis, Canad. M. A. J. 40: 34, 1939.

Forty cases of pelvic endometriosis are reviewed. The chief symptoms were abdominal pain in 30; menorrhagia or metrorrhagia in 22; and dysmenorrhea in 9. Fibroid tumors of the uterus were present in 15 instances. The rectum and sigmoid were involved either by direct invasion of endometrial adenomas or by adhesions in 23 patients. The danger of mistaking such endometrial invasion for carcinoma of the bowel is pointed out.

Treatment of pelvic endometriosis is surgical and depends on the extent of the disease. Bilateral salpingo-oophorectomy and hysterectomy was the operation performed in 32 of the 40 cases.

CARL P. HUBER

Holtz, F.: Endometrioma With Pregnancy Reaction, Gynec. et obst. 38: 278, 1939.

In endometriomas removed during various phases of the menstrual cycle, histologic study has revealed corresponding periodic changes. One would expect these transplants to assume characteristic features when they occur coincidentally with pregnancy.

Four years following the removal of the right ovary which contained a hemorrhagic cyst, probably an endometrioma, a 37-year-old primipara suffered from metrorrhagia. For relief, curettage was performed twice. She was examined nine years after the right salpingo-oophorectomy, following a two month's period of amenorrhea, and the uterus was found to be definitely enlarged and softened. In the posterior vaginal fornix, there was found a walnut-sized tumor, having the typical appearance of an endometrioma. A small portion was biopsied, and histologic examination revealed glands lined with cuboidal, epithelial cells in the secretory phase surrounded by connective tissue, having a decidual reaction. The Aschheim-Zondek test was positive, and seven months later the patient was delivered at term.

These findings demonstrate the fact that endometriomas in association with pregnancy undergo changes that correspond with those in the uterine mucosa.

ARNOLD GOLDBERGER

Hobbs, John E., and Bortnick, A. R.: Endometriosis of the Lungs, Surg. Gynec. Obst. 69: 577, 1939.

Clinical and pathologic observation, information gleaned from the literature, and a study of a series of experiments cause one to believe that endometrial tissue is transported through lymphatics and veins, and that autotransplanted uterine mucosa of the rabbit will grow in the lung tissue.

A plausible explanation for vicarious menstruation is evident, since endometrial tissue can get into the general circulation either through a patent foramen ovale or by propagation through the pulmonary circulation.

Aberrant endometrial tissue has characteristics which would indicate it has increased potentiality to become malignant.

WM. C. HENSKE.

- GEORGE MUSA, New York, N. Y.
 JOSEPH N. NATHANSON, New York, N. Y.
 CHARLES J. NEWCOMB, Milwaukee, Wis.
 ZACHARIAH B. NEWTON, Philadelphia, Pa.
 RICHARD B. NICHOLLS, Norfolk, Va.
 HAROLD G. NIX, Tampa, Fla.
 CORNELIUS T. O'CONNOR, Boston, Mass.
 ROGER O'DONNELL, JR., Washington,
 D. C.
 JAMES L. O'LEARY, Brooklyn, N. Y.
 GEORGE W. OUTERBRIDGE, Philadelphia,
 Pa.
 JOHN D. OWEN, Milwaukee, Wis.
 ERNEST W. PAGE, Berkeley, Calif.
 CHARLES W. PAVEY, Columbus, Ohio.
 EMMET A. PEARSON, Los Angeles, Calif.
 ORANGE B. POMEROY, Cleveland, Ohio.
 HOWARD A. POWER, Pittsburgh, Pa.
 RICHARD M. H. POWER, Montreal, Canada.
 WILLARD F. PRESTON, Wilmington, Del.
 EDWARD M. RANSON, Minot, N. D.
 MAURICE ROSHBAUM, New York, N. Y.
 RICHARD D. REEKIE, Spokane, Wash.
 OWEN F. ROBBINS, Minneapolis, Minn.
 FLOYD S. ROGERS, JR., Washington, D. C.
 MONROE A. ROSENBLUM, New York,
 N. Y.
 ALEXANDER H. ROSENTHAL, Brooklyn,
 N. Y.
 MILTON M. ROZAN, Lansing, Mich.
 WILLIAM P. SADLER, Minneapolis, Minn.
 JOHN E. SAVAGE, Baltimore, Md.
 THOMAS E. SCHATZ, Bethlehem, Pa.
 E. F. SCHNEIDERS, Madison, Wis.
 C. WESLEY SEWELL, Boston, Mass.
 HENRY SHACOFF, Chicago, Ill.
 HAROLD W. SHUTTER, Milwaukee, Wis.
 V. BLANCHE SLAGERMAN, Los Angeles,
 Calif.
 ROBERT P. SMITH, Seattle, Wash.
 LUCILLE H. SNOW, Evanston, Ill.
 HERBERT I. SPITZEL, White Plains, N. Y.
 HARRY L. STEWART, JR., Detroit, Mich.
 GEORGE L. STICKNEY, Baltimore, Md.
 WILLIAM E. STUDDIFORD, JR., New York,
 N. Y.
 WILLIAM D. SUGGS, Richmond, Va.
 WILLIAM W. SUTHERLAND, Paterson, N. J.
 RALPH E. TAFEL, Pittsburgh, Pa.
 JOSEPH N. TESI, New York, N. Y.
 WALTER L. THOMAS, Durham, N. C.
 OWEN J. TOLAND, Philadelphia, Pa.
 PENDLETON TOMPKINS, Philadelphia, Pa.
 HERBERT F. TRAUT, New York, N. Y.
 WARREN W. TUCKER, Denver, Colo.
 ISADORE C. UDESKY, Chicago, Ill.
 FRED VAUGHAN, New Orleans, La.
 MORTON VESELL, New York, N. Y.
 ADRIAN W. VOEGELIN, Philadelphia, Pa.
 CLIFFORD J. VOGT, Cleveland, Ohio.
 CHARLES S. WACHS, Philadelphia, Pa.
 JACOB WALKER, Philadelphia, Pa.
 WILLIAM G. WALLACE, Beaumont, Texas.
 ESTHER C. WALLNER, Louisville, Ky.
 LOFTUS L. WALTON, Hartford, Conn.
 JOSEPH G. WEBSTER, Kansas City, Mo.
 CHARLES C. WEITZMAN, Brooklyn, N. Y.
 GEZA WEITZNER, New York, N. Y.
 IRWIN WELLEN, New York, N. Y.
 LAWRENCE R. WHARTON, Baltimore, Md.
 JOSEPH R. WHERRITT, Salt Lake City,
 Utah
 HAROLD M. WILEY, Cincinnati, Ohio.
 RICHARD J. WILLIAMS, Lynn, Mass.
 WILLIAM M. WILSON, Portland, Ore.
 ARTHUR C. WOGGON, Rochester, N. Y.
 CHARLES B. WOODMAN, Morristown, N. J.

- MELBOURNE W. BOYNTON, Chicago, Ill.
 LEO BRADY, Baltimore, Md.
 WILLIAM M. BRAMS, Newark, N. J.
 PORTER BROWN, Salina, Kan.
 WILLIS E. BROWN, Ann Arbor, Mich.
 RICHARD D. BRYANT, Cincinnati, Ohio.
 JACOB L. BUBIS, Cleveland, Ohio.
 LYMAN BURNHAM, Englewood, N. J.
 CHARLES L. BUXTON, New York, N. Y.
 STANLEY M. BYSSHE, New York, N. Y.
 ALEXANDER M. CAMPBELL, Grand Rapids, Mich.
 EVERETTE L. CAMPBELL, New York, N. Y.
 JAMES V. CAMPBELL, Oakland, Calif.
 JAMES C. CAREY, Joliet, Ill.
 WILLIAM V. CAVANAGH, New York, N. Y.
 CHARLES E. CAVERLY, New York, N. Y.
 PHILLIPS K. CHAMPION, Dayton, Ohio.
 HOWARD C. CLARK, Wichita, Kan.
 LAWRENCE L. COCKERILLE, Washington, D. C.
 MELVIN R. COHEN, Chicago, Ill.
 CONRAD G. COLLINS, New Orleans, La.
 SIDNEY B. CONGER, Akron, Ohio.
 BENJAMIN F. CORNWALL, Salem, Mass.
 JOSEPH E. CORR, New York, N. Y.
 MARGARET D. CRAIGHILL, Greenwich, Conn.
 THOMAS E. CULLITON, Lynn, Mass.
 WILLIAM G. CUMMINGS, Evanston, Ill.
 M. Y. DABNEY, Birmingham, Ala.
 VIRGIL G. DAMON, New York, N. Y.
 DAVID M. DAVIDOW, Detroit, Mich.
 JACHIN B. DAVIS, New Haven, Conn.
 ALLEN L. DECAMP, Fayetteville, N. C.
 EDWIN J. DECOSTA, Chicago, Ill.
 EDWARD M. DORR, Chicago, Ill.
 ROBERT G. DOUGLAS, New York, N. Y.
 JOSEPH W. DRAPER, New York, N. Y.
 JOHN H. DUGGER, Philadelphia, Pa.
 JOHN C. DUMLER, Baltimore, Md.
 CHRISTOPHER J. DUNCAN, Brookline, Mass.
 F. SIDNEY DUNNE, Philadelphia, Pa.
 ROBERT G. M. DUNOVANT, New York, N. Y.
 SYDNEY ELLIS, Boston, Mass.
 RAYMEN G. EMERY, Washington, Pa.
 ALFRED C. EMMEL, Mt. Vernon, N. Y.
 JACOB EPSTEIN, Rochester, N. Y.
 HOUSTON S. EVERETT, Baltimore, Md.
 RUTH E. EWING, New York, N. Y.
 ARTHUR M. FARIS, Houston, Texas.
 DAVID P. FINDLEY, Omaha, Neb.
 WILBUR EUGENE FISHER, Washington, Pa.
 WILLIAM J. FITZGERALD, Albany, N. Y.
 ABRAHAM J. FLEISCHER, New York, N. Y.
 JAMES LOUIS FLEMING, Chicago, Ill.
 JOHN G. FLEMING, Cincinnati, Ohio.
 JOSEPH A. GAINES, New York, N. Y.
 PERCY B. GALLEGOS, Stockton, Calif.
 THOMAS K. GALVIN, Baltimore, Md.
 JOHN R. GEFFERT, New York, N. Y.
 ELMER GERGELY, Brooklyn, N. Y.
 HENRY H. GIBSON, Akron, Ohio.
 WILLARD M. GREEN, Pontiac, Mich.
 ANDREW M. GROSECLOSE, Roanoke, Va.
 PAUL GUSTAFSON, Boston, Mass.
 ALAN F. GUTTMACHER, Baltimore, Md.
 BRUCE A. HARRIS, Brooklyn, N. Y.
 CLAUDE E. HEATON, New York, N. Y.
 JOSEPH V. HEIMANN, Lakewood, Ohio.
 J. CURTIS HELLRIGEL, Scranton, Pa.
 HERMAN HERTZBERG, Washington, D. C.
 LOWELL R. HILL, Long Beach, Calif.
 DAVID S. HILLIS, Chicago, Ill.
 CLAYTON H. HIXSON, Washington, D. C.
 JOHN W. HOFMANN, Indianapolis, Ind.
 KERCHIVAL R. HOLT, Hartford, Conn.
 LLOYD L. HOSKINS, Cleveland, Ohio.
 CRAIG S. HOUSTON, Providence, R. I.
 J. MASON HUNDLEY, Jr., Baltimore, Md.
 LEWIS P. JAMES, Hartford, Conn.
 C. N. JEFFRIES, Mamaroneck, N. Y.
 AUSTIN B. JOHNSON, Far Rockaway, N. Y.
 HARRY L. KAVA, Flushing, N. Y.
 JOHN A. KELLY, New York, N. Y.
 DAVID C. KIMBALL, Detroit, Mich.
 HARRY KIRSCHBAUM, Detroit, Mich.
 JACOB KOTZ, Washington, D. C.
 ERNEST W. KULKA, New York, N. Y.
 RAPHAEL KURZROK, New York, N. Y.
 DAVID H. KUSHNER, Washington, D. C.
 WALTER J. LARKIN, Scranton, Pa.
 ELISABETH LARSSON, Beverly Hills, Calif.
 THOMAS E. LAVELL, New York, N. Y.
 BENNO LIEGNER, New York, N. Y.
 BRUCE V. MACFADYEN, Philadelphia, Pa.
 LOCKE L. MACKENZIE, New York, N. Y.
 JOHN J. MADDEN, Brooklyn, N. Y.
 REGINALD D. MARGESON, Brookline, Mass.
 JAMES P. MARR, New York, N. Y.
 THOMAS B. MARWIL, Detroit, Mich.
 CHARLES H. MAUZY, Jr., Winston-Salem, N. C.
 MAX D. MAYER, New York, N. Y.
 JOHN C. McDERMOTT, Los Angeles, Calif.
 ROBERT C. McDOWELL, Buffalo, N. Y.
 D. C. MCGILL, Rochester, N. Y.
 CHARLES H. MCKENZIE, Minneapolis, Minn.
 ROBERT F. MONROE, Louisville, Ky.
 JAMES R. MONTGOMERY, White Plains, N. Y.
 FRANK MOSKOWITZ, Brooklyn, N. Y.
 EARL R. MUNTZ, Ada, Okla.

- New England Obstetrical and Gynecological Society.** *President*, Thomas Almy. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, Alice F. Maxwell. *President-Elect*, John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. Next meeting, San Francisco, Calif., Nov. 6 to 9, 1940.
- Washington Gynecological Society.** *President*, H. P. Ramsey. *Secretary*, James R. Costello, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, H. C. McGee. *Secretary*, H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, Percy H. Swahlen. *Secretary*, Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Floyd Bell. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, H. Reid Robinson, Galveston, Texas. *Secretary-Treasurer*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Marlin, Texas, October, 1940.

Books Received

FUNDAMENTALS OF INTERNAL MEDICINE. By Wallace Mason Yater, professor of medicine and director of the department of medicine, Georgetown University School of Medicine, etc. First edition—revised. 1021 pages with 254 illustrations. D. Appleton-Century Company, New York, 1940.

SYNOPSIS OF SURGERY. By H. E. Mobley, M.D., F.A.C.S., chief of surgery at St. Anthony Hospital, Morrilton, Arkansas. 375 pages with 339 text illustrations including 39 in color. The C. V. Mosby Co., St. Louis, 1940.

SYNOPSIS OF OBSTETRICS. By Jennings C. Litzenberg, professor emeritus of obstetrics and gynecology, University of Minnesota Medical School, Minneapolis. 394 pages with 157 illustrations including 5 in color. The C. V. Mosby Co., St. Louis, 1940.

CYCLOPROPANE ANESTHESIA. By Benjamin Howard Robbins, associate professor of pharmacology, Vanderbilt University School of Medicine. 175 pages, illustrated. Williams & Wilkins Company, Baltimore, 1940.

CONGENITAL MALFORMATIONS. By Douglas P. Murphy, assistant professor of obstetrics and research associate in the Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. University of Pennsylvania Press, Philadelphia, 1940.

SPECIALTIES IN MEDICAL PRACTICE. Edited by Edgar van Nuys, chief of a section in the division of medicine, The Mayo Clinic, Rochester, Minn. etc., with a Foreword by Donald C. Balfour, consultant in surgery, The Mayo Clinic. Loose-Leaf, in two volumes, illustrated. Thomas Nelson and Sons, New York, 1940.

BIOLOGICAL SYMPOSIA. Edited by Jaques Cattell, editor of The American Naturalist and American Men of Science. 238 pages, illustrated. The Jaques Cattell Press, Lancaster, Pa., 1940.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, E. J. Litzenberg. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June, 1941, Colorado Springs, Colo.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, James R. McCord. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.
- Central Association of Obstetricians and Gynecologists.** *President*, Jennings C. Litzenberg, Minneapolis, Minn. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, M. P. Rucker, Richmond, Va. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Norman F. Miller, Ann Arbor, Mich. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1941, Cleveland, Ohio.
- New York Obstetrical Society.** *President*, Thomas C. Peightal. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Roy W. Mohler. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill., Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, Frances Doyle. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue.
- Baltimore Obstetrical and Gynecological Society.** *President*, N. J. Eastman. *Secretary*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Dr. Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, April, and June.
- Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

within certain limits, this is undoubtedly influenced by the amount of vitamin in the diet.⁹ Vitamin B₁ cannot be synthesized in the normal processes of the human body.

The dependence of the urinary excretion of vitamin B₁ upon the dietary intake has been investigated by several workers.^{10, 11} Robinson and his co-workers found recently that urinary excretion levels can, under proper conditions, be used as an index of thiamin nutrition in human beings. They also reported good correlation between urinary thiamin excretion and the adequacy of vitamin B₁ in the preceding diet. Deficiency symptoms of nutritional origin have been found associated with low excretion levels, and with poor excretion response to test doses. With suitable practical methods, the concentration of vitamin B₁ in the body tissues, blood and excretory products may be determined; and requirements necessary to maintain normal health or to treat deficiency diseases in the human being may be established. At present clinical response is the best test for adequacy of dosage in such conditions.

Vitamin B₁ is associated with the intermediary metabolism of carbohydrates.^{12, 13} The pyrophosphoric acid ester of vitamin B₁ acts as a co-enzyme (co-carboxylase) to activate carboxylase which catalyzes pyruvic acid, a conversion product of lactic acid. If the pyruvic acid is destroyed by oxidation, the presence of co-carboxylase is again necessary as it acts here as a co-ferment with oxidase.

The need of an increased intake for growth of young rats has been demonstrated, as well as a similar need in female rats at puberty. The gastrointestinal tract responds to a vitamin B₁ deficiency with an anorexia, a depression of the acid secreting response of the gastric glands, and an atony of the intestines.

In the physiology of the heart muscle, Weiss and Wilkins¹⁴ point out that thiamin chloride acts as an acceptor, causing the oxygen to unite with the carbohydrate and amino acids delivered to the cell by the blood and lymphatic circulation, increasing the rate of intracellular metabolism, so that the metabolic process is nearer to the end point of the cell oxidation process.

The best animal sources¹⁵ of vitamin B₁ include pork, other muscle and organ foods, while egg yolk, chicken, fish, and milk are poor sources, but milk may be regarded as an important source of supply, since it need not be processed, and because it is usually used in fair quantities. The richest vegetable supply lies in whole grain cereals, legumes, and nuts. While other vegetables, including potatoes, may be fair sources of vitamin B₁, the usual disregard of nutrient losses in cooking causes them frequently to be depreciated markedly in value. Although fruits in general have a low content, the fact that they are eaten raw serves to offset any possible loss in cooking. Not alone is the manner of cooking an element in producing vitamin B₁ deficiency, but the processing of the generally used white flour removes a large available amount through loss of wheat germ and bran which normally make whole grain one of the most important sources of supply.

The modern American diet has been regarded as deficient in many respects, due in part to faulty dietary habits and food selections based largely on appearance or taste, often leading to a high carbohydrate intake and an excess of fat. Again, economic status plays a part and, in an effort to provide sufficient calories in energy foods at low cost, a carbohydrate diet prevails. Voluntary faddish restrictions in diet, for supposed allergies, for weight reduction, or through misleading advice, lead to marked inadequacies in dietary essentials. Organic or functional disease may interfere with both absorption and utilization and bring to light latent deficiency conditions.

Stiebeling and Phipard,¹⁶ in their analysis of diets of families of employed wage earners in eight major geographic areas of the United States, have de-

American Journal of Obstetrics and Gynecology

VOL. 40

AUGUST, 1940

No. 2

Original Communications

THE RELATION OF VITAMIN B₁ TO THE REPRODUCTIVE CYCLE*

CORRELATION BETWEEN VITAMIN B₁ CONTENT OF DIET AND ELECTRO-
CARDIOGRAPHIC FINDINGS IN 91 PREGNANT WOMEN

PHILIP F. WILLIAMS, M.D., GEORGE C. GRIFFITH, M.D., AND
FLORENCE G. FRALIN, B.S., PHILADELPHIA, PA.

THE story of vitamin B₁ is an interesting chapter in medical science¹ and covers the notable discovery of Eijkman,² the researches of Funk,³ Jansen and Donath,⁴ and, more recently, the complete synthesis of thiamin by Williams and Cline.⁵ The chemical structure of vitamin B₁ (thiamin) is now known, and it has been isolated in the form of its chloride hydrochloride.

The international unit of vitamin B₁ has been defined (1938) as the antineuritic activity of 3 micrograms of the international standard preparation of crystalline vitamin B₁ hydrochloride. One milligram of thiamin chloride is equivalent to 333 international units of vitamin B₁. The Council on Pharmacy and Chemistry of the American Medical Association has allowed certain claims for thiamin chloride, and practically all these may find place in obstetric practice.

It is generally accepted that this dietary essential has an important role in the functioning of every cell, rather than in the activity of a special organ or tissue system.⁶ Storage of vitamin B₁ appears to be of a limited order. The heart, liver, and kidney of experimental animals apparently have the highest content^{7, 8} under normal conditions and,

*Read, by invitation, at a meeting of the Pittsburgh Obstetrical and Gynecological Society, May 15, 1940.

This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

Boerma,²⁰ whose observations were made in Java, believes that beriberi, appearing during pregnancy, is conditioned by the vomiting, and is more severe if a serious illness has preceded the pregnancy. While the evolution of the pregnancy is not hindered by the beriberi, it is his view that the greatest danger to the woman came from a cardiac insufficiency during delivery. Balfour and Tolpade, quoted by Guggisberg,²¹ state that every pregnant woman in South India suffers from beriberi. The extremely high maternal mortality in these women is caused by a macrocytic type of anemia which is quickly improved by yeast, liver extract, and a meat diet, all of which are rich in the vitamin B complex.

From Japan, Fujita²² reported 39 cases of pregnancy and beriberi under his care, the beriberi appearing late in pregnancy or in the puerperium, and more frequently in summer or autumn. The regional mortality of the combined conditions ranges from 9 to 15 per cent, and although only one mother in Fujita's series died, approximately 25 per cent of the babies were lost. In the Philippine Islands, a high neonatal mortality rate has been ascribed by Andrews²³ to an infantile beriberi due to a deficiency of the growth and nerve development factors of the mother's milk.

One of the notable clinical manifestations of a deficiency in vitamin B₁ is the polyneuritis of pregnancy, which sometimes accompanies severe hyperemesis gravidarum.

Luikart,²⁴ Plass and Mengert,²⁵ and Strauss and McDonald²⁶ have ably demonstrated this relationship and the therapeutic effectiveness of vitamin B₁. With the synthesis of thiamin the more advantageous parenteral route of administration has been made possible. Here the therapeutic dose depends upon the clinical reaction to measured amounts of the remedy.

In one instance Hildebrandt and Otto²⁷ gave 1,782 mg. of vitamin B₁ during a pregnancy complicated by a severe polyneuritis. There was no toxic reaction to the drug, and no excretion of the vitamin in the urine up to the time of delivery. Evidently the demand did not permit saturation even with so large an intake.

On the other hand deleterious effects on reproduction of very large doses of vitamin B₁ may be possible.

Sure²⁸ demonstrated that in rats fed 100 micrograms of thiamin daily, sterility occurred in the females of the second generation. Continuing this study it was found that a daily dose of 400 micrograms produced entire failure of lactation in the third generation.

Saturation tests, according to Neuweiler,²⁹ show that pregnant women tend to retain a large proportion of a parenteral dose of vitamin B₁, especially if any manifestations of toxemia are present. Since it appears in certain such instances that saturation with subsequent excretion of vitamin B₁ in the urine may be difficult to obtain, an attempt should be made to reach an excretion-producing dosage before considering that this type of treatment has been adequately used, unless clinical improvement has appeared.

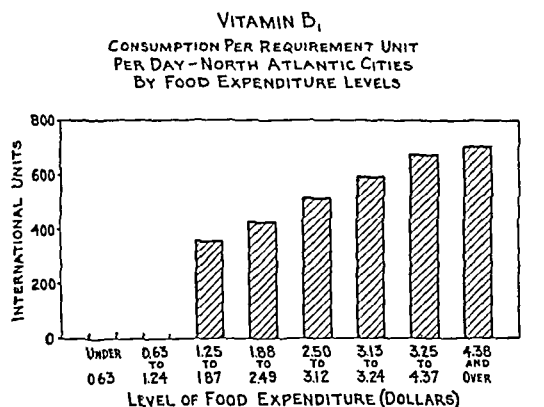
The frequent occurrence of a hypochromic macrocytic anemia in pregnant women suffering with beriberi, or a less marked vitamin B₁ deficiency, has pointed to a similar etiology of the two conditions. Although marked improvement has followed the use of vitamin B₁ containing substances in this type of anemia, it is by no means definitely proved that lack of this factor alone is the cause. According to Elsom,³⁰ the deficiency in the diets of such anemic women probably concerns the entire B complex.

terminated the vitamin B₁ content. The average vitamin B₁ content of these diets gradually increases with rising weekly expenditures for food. Since both Pittsburgh and Philadelphia are included in Stiebeling and Phipard's North Atlantic area, the observations for this area alone will be considered (Fig. 1).

With food expenditures of \$1.25 to \$1.87 per capita per week, the average vitamin B₁ content of food per person reached only 290 international units. It was not until the food cost reached an expenditure of \$3.13 to \$3.74 that the allowance of 500 international units was reached.

It was estimated that one-fourth of all white families in the entire survey received less than 400 international units of vitamin B₁ per adult per day. About 10 per cent selected food furnishing less than 300 units, and only half obtained the 500 unit allowance set for an adult per day. Their study was made in families of only employed wage earners, and therefore the vitamin B₁ values received by the families where there was unemployment or relief is left to conjecture.

We have been able to find only one reference in the literature to an analysis of vitamin B₁ in the diets of pregnant women. McCance, Widdowson and Vernon-Roe,¹⁷ in a study in England found that the vitamin B₁ value of the diets advanced as food expenditures rose. Only the maximum intakes of the three highest income groups studied revealed over 500 international units, while the minimum intake for all groups fell below 300 international units.



NOTE—ADAPTED FROM STIEBELING & PHIPARD

Fig. 1.

We may examine the recent report of Jolliffe¹⁸ who agrees with Strauss¹⁹ that beriberi is endemic in this country. Jolliffe regards the present daily American dietary as containing from 300 to 450 international units of vitamin B₁, and discusses the faults of a national diet which results in an annual per capita consumption of 100 pounds of sugar and white flour made from 4 bushels of wheat. These two sources, which furnish 55 per cent of the daily average of 2,500 calories, do not contain more than 50 international units of vitamin B₁.

The safety margin above a beriberi level of Sherman's average American diet according to Jolliffe¹⁸ is only 20 per cent by the Cowgill ratio. Jolliffe's analysis of diets in 1,394 North American families by the same means shows interesting results. According to certain levels of food expenditure the safety factor ranged from 3 to 25 per cent. It is apparent that the entrance of a single disturbing factor may obliterate this scant margin of safety and bring on the clinical symptoms of a deficiency. In this light, Jolliffe regards gestational neuritis as a misnamed appearance of beriberi.

Beriberi, endemic in the Orient, has afforded an opportunity to witness the interrelationship of severe degrees of vitamin B₁ deficiency and pregnancy.

inertia and subinvolution. The same effects were seen by Moore and Brodie,³¹ who noted, in addition, that deaths during the nursing period were caused by hemorrhages, while myelin degeneration of the vagus and phrenic nerves was present. Before death such young rats exhibited signs of advanced beriberi. Commenting on his own animal work and its relation to the human organism, Shin³⁷ describes an infant which exhibited classical signs of beriberi when only two days old. He states that at times the newborn infant may show evidence of the disease before the mother, on a vitamin B₁ deficient diet, had developed the puerperal lesions so frequently seen in his district in China.

The metabolism of vitamin B₁ in relation to the human reproductive cycle has been studied only recently. The function of the placenta as a place of storage has been questioned.

Stahler³⁸ believes that the placenta is permeable to this vitamin since the blood of infants showed a concentration similar to that of the mother, even though the latter had been given intramuscular injections of vitamin B₁ just before labor. Guggisberg²¹ also regards the placenta as a filter which permits the demands of the fetus to be adequately withdrawn. He remarks that vitamin B₁ distinguishes itself as an element of low storage capacity and that, without marked reserves in other parts of the body, the placenta finds no sufficient reserve stores to seize and place at the disposal of the fetus. Stahler also showed that the expressed extract of the placenta contained less vitamin B₁ proportionately than the fetal blood.

Dubrausky and Lajos,³⁹ however, believe that the placenta is a reservoir and plays an active part in supplying the fetus. They found that the vitamin B₁ content of the placenta fluctuated between 108 micrograms per cent and 980 micrograms per cent. Since this was greater than the value of either the maternal or fetal blood, as they determined them, it might seem that their conclusion was well supported.

The requirement of this vitamin for the human being has been a matter of considerable discussion. The experiments of Osborne and Mendel years ago indicated that there was a greater need as the size of the body increased. In recent years a relationship of the vitamin B₁ requirement to the caloric intake has been recognized.

Cowgill,⁴⁰ by determining the minimum vitamin B₁ requirement of the mouse, rat, dog, and pigeon, found that he could express the minimum requirement in terms of units of body weight and metabolism. His formula for the human being may be expressed as follows:

$$\frac{\text{Vitamin (daily requirement of vitamin B}_1\text{)}}{\text{Calories (daily total energy exchange)}} = K (\text{weight in kilograms}) \times 0.0284.$$

The result was expressed in milligram equivalents of his standard test powder. Since the adoption of the Standard International Unit in 1938 as the potency of 3 micrograms of thiamin chloride, the weight in kilograms must be multiplied by a human species constant of 0.00426 to obtain the requirement in the present international unit. It should be understood that such needs represent only the minimum or beriberi preventing level.

Cowgill states that, in view of the relationship of the vitamin B₁ requirement to the caloric intake, a simple form of standard to express the vitamin B₁ need is the number of units per hundred calories. Stated in this manner his minimums are approximately 10 international units per 100 calories for a normal human adult. Rose⁴¹ recommended 15 international units per 100 calories, and Daniel and Munsell⁴² point out that this would mean roughly 250 to 400 international units

Only a few complications caused by vitamin B₁ deficiency have been noted in connection with human parturition.

Moore and Brodie³¹ noted abnormally profuse hemorrhage during a precipitate delivery in a woman whose diet was markedly deficient in vitamin B. The baby died of hemorrhage and at autopsy gross and microscopic changes resembled those in experimental animals on a deficiency diet. There was no evidence of disease of the hematopoietic system.

The toxemias of late pregnancy have been ascribed to a vitamin B₁ deficiency.

Siddall³² advances the theory, based upon his observations on prenatal cases afflicted with beriberi in China, that normal function of the pituitary gland is possible only when an adequate supply of vitamin B₁ is available. He believes that in the pregnant woman a deficiency leads to an over-compensation or malignant hyperfunction of the gland. This in time produces the various symptoms of toxemia; disturbed carbohydrate metabolism, edema, elevated blood pressure, nausea and vomiting, and an increase in prolactin and decrease in estrin. According to this theory an adequate and constant supply of vitamin B₁ should prevent toxemia and perhaps cure it. In view of the saturation excretion data already considered, it may be that the doses of synthetic vitamin B₁ which were used in the clinical studies based upon this hypothesis were inadequate as curative therapy. On the other hand the pituitary change may have been too well established to have been influenced rapidly.

Yasunami³³ in a recent contribution from Japan found in his toxemia cases, mostly from a group with low living conditions, that treatment with vitamin B₁ in large doses was very effective, especially, in avoiding convulsions in the pre-eclamptic patients. Ross and his co-workers³⁴ in a dietary study in North Carolina, however, failed to note a decrease in the incidence of toxemia during the latter part of pregnancy in a controlled group of patients who received an adequate amount, approximately 1,000 international units of vitamin B₁ in the form of yeast tablets daily.

As to the relationship between vitamin B₁ deficiency and the toxemias, Vignes³⁵ remarks upon the diminution in volume of the liver observed in the deficiency cases, the diminution of glycogen in this organ and the muscles, and a reduction in the tolerance of carbohydrates. The latter, not being transformed into glycogen, encumber the blood as an excess of glucose, a hyperglycemia resulting. Much has been written on the role of vitamin B₁ in the metabolism of carbohydrates, and not a few obstetric authors today recommend supplemental administration of vitamin B₁ during therapy with large or continued injections of dextrose or glucose.

The minor paresthesias and neuritides of the extremities and back complicating pregnancy and the puerperium have responded quickly in many instances to vitamin B₁ therapy. Stillbirths were observed in a number of cases of pregnancy complicated by nutritional deficiencies in Vignes' clinic, and he regards a vitamin B₁ deficiency as frequently responsible for sterility, abortion, and ineffectual labors with post-partum inertia and hemorrhage.

Subsequent to these clinical observations Ueno³⁶ has shown by animal experiments that marked changes in the reproductive cycle follow a vitamin B₁ deficiency diet. White rats developed a stationary sexual stage, and even matings with normally fed rats failed in high percentage. The development of fetuses in the successful matings was hindered, and abortion and resorption were frequent. Fetuses born alive were small and weak. Labors were characterized by

a period of seven days. There was a second interview during which the food record* was scrutinized and checked and the patient was scheduled for an electrocardiogram. We feel that the food records, obtained in the manner described, furnish a reasonably good picture of the usual diets of these pregnant women. An estimate of the food value was made from these records and the vitamin B₁ values were recorded in terms of international units, in most instances as set forth in *Food Values of Portions Commonly Served*, Second Edition, 1940, prepared by Bowes and Church.⁵¹

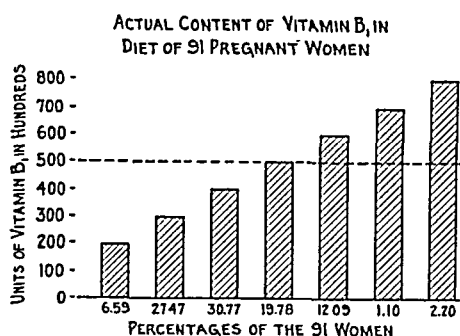


Fig. 2.

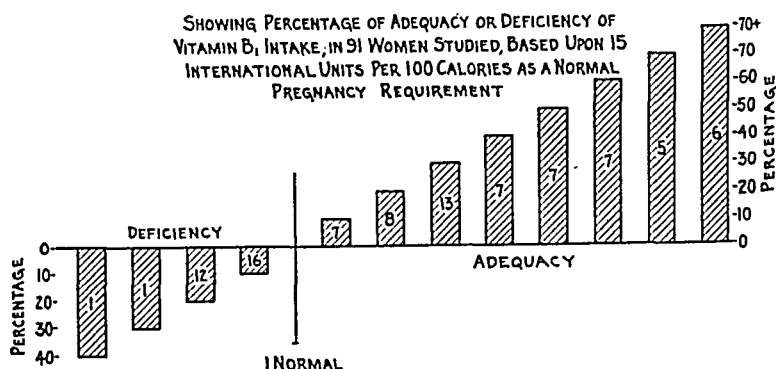


Fig. 3.

The vitamin B₁ values were computed for a great many foods on the basis of the fresh, raw state, depending upon the availability of the data. No attempt was made to determine cooking losses, since these vary with the method followed. When wide ranges in vitamin B₁ value were reported, the lowest value was chosen arbitrarily, since we did not know which value represented the greater number of assays.

The vitamin B₁ values of these diets have been arranged graphically to show the actual content in hundreds of international units. This chart shows the percentages of vitamin B₁ values in relation to the suggested daily requirements of 500 international units for a normal adult set by Stiebelling and Phipard.¹⁶ It serves to indicate how deficient the diets of these women must be when it is generally agreed that the requirements are higher during pregnancy and lactation (Fig. 2).

*The forms used for the food analyses were patterned after those designed for teaching purposes at the Dental School of the University of Pennsylvania.

per day for an adult. According to Cowgill⁴³ it appears that adults require a daily minimum approximately 300 to 350 international units of the vitamin, which is equivalent to about 1 mg. of thiamin. Vorhaus, Williams, and Waterman⁴⁴ have calculated the same amount as the vitamin B₁ requirement of the normal adult. Stiebeling and Phipard in a survey of diets in the United States set 500 international units as the daily allowance of "per requirement units," for an adult of twenty years or more. Recently, Williams and Spies,¹ in discussing the vitamin B₁ sparing action of fat, prefer to use the ratio T(thiamin)/non-fat calories, to determine the margin of protection against beriberi in various diets.

The majority of workers in the field of nutrition agree that the requirements for pregnancy are decidedly higher than for a nonpregnant individual. Vignes is of the opinion that the increased requirement of the pregnant woman is conditioned principally by demands of the fetus.

In pregnancy many of the factors regarded as ordinarily increasing the requirement are present: growth of the fetus, reserve growth, increase in metabolism (the increase in the basal metabolic rate may be attributed largely to fetal metabolism), increased urinary excretion, interference with proper alimentation, in early pregnancy due to the vomiting and in late pregnancy due to displacement of the gastrointestinal tract. There are, of course, the ever present factors of economy, ignorance, and misguidance in selection of food.

The Health Committee of the League of Nations⁴⁵ proposed in their nutritive requirements for pregnancy that 150 to 250 international units of vitamin B₁ are essential. Cowgill⁴⁶ regards these requirements as inadequate. He suggests a daily intake for the American mother of not less than 15 and preferably as high as 20 international units per 100 calories, for a 2,500 caloric intake, 375 to 500 international units. Dieckmann⁴⁷ sets 400 international units for the first twenty-eight weeks, then 600 international units to term. Rose believes that pregnant women should have double the quantity of vitamin B₁ required by the normal adult. Baker and Wright⁴⁸ recommended an intake during pregnancy of three to five times the requirement of the nonpregnant state.

In a series of pregnant women studied in Holland, Westenbrink and Goudsmit⁴⁹ found a lowered excretion of vitamin B₁, even when there was a supplemental intake, as compared with nonpregnant women on the same diet. With few exceptions there was no evidence that the pregnant women were saturated with vitamin B₁. Such work on saturation and urinary excretion tests appear to support the ideas regarding increased requirements of vitamin B₁ during pregnancy and its complications. Gaetgens⁵⁰ believes pregnancy does not increase the vitamin B₁ need. He states that the average of 1 mg. of aneurin (thiamin) which is required for a normal male adult should be sufficient for a pregnant woman.

In the course of a nutrition survey begun in Philadelphia last year, using over 500 pregnant women in various prenatal clinics as subjects, a study of vitamin B₁ in the diets of certain of these women developed as an interesting outgrowth. We decided to estimate the dietary intake of vitamin B₁ and correlate it with electrocardiographic findings as well as with clinical deficiency symptoms and some obstetric factors. Ninety-one patients attending the prenatal clinic of the Presbyterian Hospital were studied, and there was no special selection on the basis of stage of pregnancy or degree of parity. A nutritionist interviewed each woman and instructed her in the proper method of recording food intake over

ciated or not with beriberi, he has determined a relationship between the vitamin B₁ caloric ratio and the body weight. On such a chart we have set out the individual instances of our study group. The line 40 repre-



Fig. 5.—Electrocardiographic abnormalities in vitamin B deficiency. P-wave normal, QRS slurred in the descending limb of R. T-wave rises slowly and is flattened.

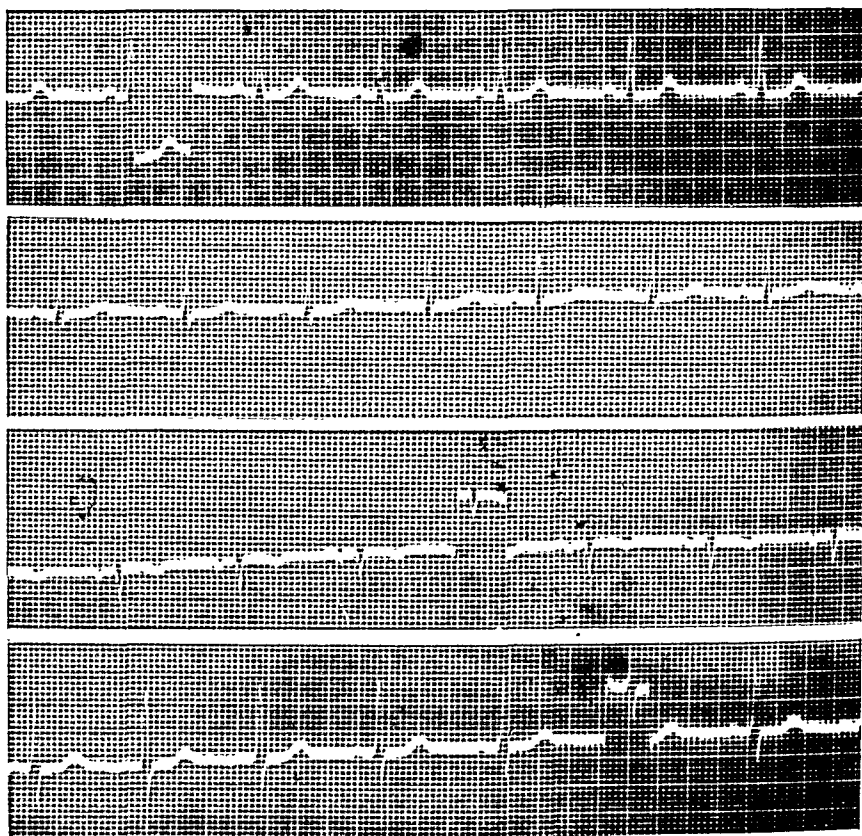


Fig. 6.—Typical tracing showing vitamin B₁ deficiency.

sents the beriberi, preventing level of the diets studied by Cowgill. The chart represents the vitamin B₁/caloric ratio of the diets plotted against the weight in kilograms.

The margin of safety of a diet against beriberi is, of course, the percentage of the vitamin B₁/caloric ratio above the minimum level for a particular weight. This has been computed for each one of the group,

It is recognized that the need for vitamin B₁ depends upon the caloric intake, and Cowgill states that a pregnant woman requires 15 international units per 100 calories. Applying this ratio, we have found the relationship of the requirement to the actual intake of vitamin B₁ expressed in Fig. 3. Practically one-third of the group was not receiving an adequate amount of vitamin B₁.

Considering moderate to marked nausea and vomiting as a vitamin B₁ deficiency symptom, 30 per cent of the patients showing inadequate intake exhibited this symptom as contrasted with 10 per cent of the

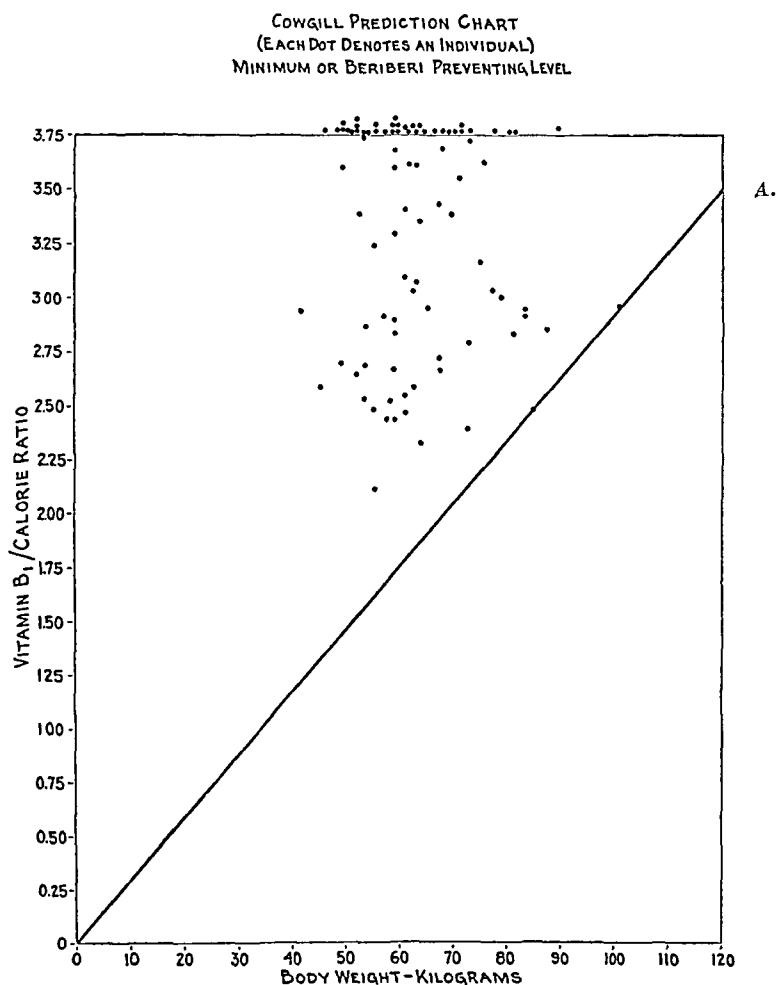


Fig. 4.

patients who had sufficient. Practically, a similar distribution of other vitamin B₁ deficiency symptoms, as fatigue, paresthesias, cramps, and dyspnea, was found. The clinical data were secured from histories recorded by disinterested persons, and, therefore, the information obtained from patients was unbiased. Still, we feel that in a relatively small series, no definite conclusions should be drawn concerning such deficiency symptoms.

A third calculation has been made possible by the use of the Cowgill prediction chart (Fig. 4). By an analysis of diets known to be asso-

Cowgill prediction chart (Fig. 4), 7 of these 8 women had a margin of safety of less than 100 per cent above the beriberi level. The lowest margin of safety was 54 per cent and the highest 143 per cent.

SUMMARY AND CONCLUSIONS

Vitamin B₁ or its synthetic equivalent, thiamin chloride, has been shown to be a dietary factor essential to the normal human adult.

The literature indicates that the requirement for this vitamin is definitely increased in pregnancy.

The effects of an outstanding deficiency, beriberi, on pregnancy have long been recognized in the Orient, yet many subclinical deficiencies in this part of the world have been mislabeled as direct results of the gestation itself.

Many workers in the fields of nutrition have shown that the average American diet provides an insufficient margin of safety against beriberi prevention.

An index of the need for and of the metabolism of thiamin chloride by saturation excretion experiments has been recently established.

Not only have the toxemias of late pregnancy been explained on a theoretical basis of vitamin B₁ deficiency, but, practically, in the Orient they have been shown to be amenable to vitamin B₁ therapy.

Animal experimentation has demonstrated the inimical effect of a vitamin B₁ deficiency upon the reproductive cycle.

Evidence has accumulated to show that the placenta acts only as a filter in the maternal fetal transference of this substance.

Our studies of the food records showed that one-third of a group of 91 pregnant women were not receiving an adequate amount of vitamin B₁, calculated on a ratio of 15 international units per 100 calories.

Practically two-thirds of this group were receiving less than 500 units of vitamin B₁, the standard followed by Stiebeling and Phipard.

There was some positive correlation between the inadequacy of the intake and deficiency symptoms, such as excessive nausea and vomiting, fatigue and paresthesias.

The margin of safety above a beriberi level as calculated on a Cowgill prediction chart ranged from 0 to 180 per cent. One-fourth had a margin of safety under 50 per cent, and two-thirds presented one under 100 per cent.

The electrocardiograms of 8 women in the group showed changes signifying a vitamin B₁ deficiency. There was no positive correlation between these electrocardiograms and the adequacy of the vitamin B₁ intake.

REFERENCES

- (1) *Williams, R. R., and Spies, T. D.*: Vitamin B₁ and Its Use in Medicine, New York, 1938, The Macmillan Co.
- (2) *Eijkman, C.*: Arch. f. path. Anat. 148: 523, 1897.
- (3) *Funk, C.*: J. Physiol. 43: 395, 1911.
- (4) *Jansen, B. C. P., and Donath, W. F.*: Mededeel. v. d. dienst. d. volksgezondh. in. Nederl.-Nidië 16: 186, 1897.
- (5) *Williams, R. R., and Cline, J. K.*: J. Am. Chem. Soc. 58: 1504, 1936.
- (6) *Cowgill, G. R.*: The Physiology of Vitamin B₁, The Vitamins, Chicago, 1939, American Medical Association.
- (7) *Westenbrink, H. G. K.*: Arch. neerl. de physiol. 17: 560, 1932.
- (8) *Graham, C., and Griffith, W. H.*: Proc. Soc. Exper. Biol. & Med. 29: 695, 1932.
- (9) *Brodie, J. L., and MacLeod, F. L.*: J. Nutrition 10: 179, 1935.

and the range was found to extend from 0 to 180 per cent. The percentages of the margin of safety have been plotted out in Fig. 7. It will be seen that about one-fourth have under a 50 per cent, and two-thirds under a 100 per cent margin of safety.

When the histories of the 91 women with the lowest margins of safety were reviewed, it was found that 5 had had marked to excessive nausea and vomiting of pregnancy, and in addition 1 had had mild neuritis.

After analyzing our food records, we began a correlation between any possible cardiac lesions as revealed by the electrocardiograph, and the actual content of vitamin B₁ in the diets.

Electrocardiographic studies in the vitamin B₁ deficient hearts have been characteristic in that the rate is usually slow and the voltage low. There is a slight slurring of the descending limb of the R-wave, a slowly rising, round T-wave, and a prolongation of the P-Q interval. A diagrammatic drawing of a typical vitamin deficient QRS and T-wave is

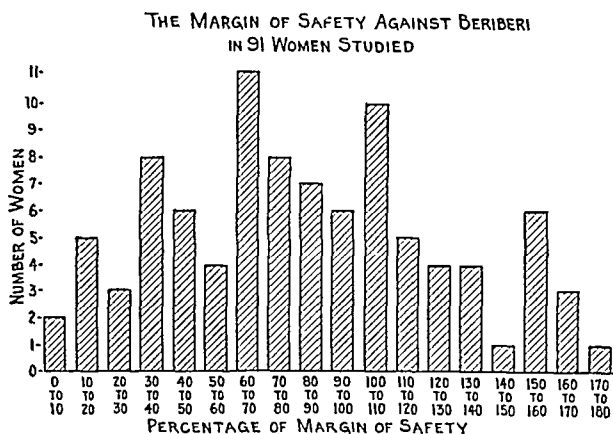


Fig. 7.

shown in Fig. 5. Weiss and Wilkins,⁵² in their work on the "nature of cardiovascular disturbances in nutritional deficiency states," have demonstrated similar electrocardiographic changes in a study of vitamin deficient rats.

Of the 91 electrocardiograms studied, 8 showed characteristic changes mentioned above. In no one of these was there any history or physical signs relating to previous cardiac disease. A typical tracing showing vitamin B₁ deficiency is illustrated in Fig. 6. When we reviewed the vitamin content of the diets of these 8 women at the time the electrocardiogram was made, we found that, according to the ratio of 15 international units to 100 calories, 4 were deficient, and 4 had an adequate amount of vitamin B₁ in the diet. One case, however, had only a plus 2 per cent adequacy. In this connection Weiss remarks that he has observed patients with histories of vitamin B₁ deficiency in whom the only detectable objective change was in the electrocardiogram.

There was no correlation observed between the significant electrocardiograms and various other deficiency symptoms. According to the

ABDOMINAL PREGNANCY*

CLIFFORD B. LULL, M.D., PHILADELPHIA, PA.

IMPREGNATION of the human ovum does not always result in an intrauterine gestation. I wish to limit my discussion to those tragic cases where the impregnated ovum, either through the process of tubal abortion or rupture, attaches itself and continues to grow in the peritoneal cavity, this viewpoint being taken because of the improbability of the occurrence of primary abdominal pregnancy. I should also like to confine my discussion to those cases which develop in the abdominal cavity as a secondary pregnancy beyond the sixth month, up to and approaching full term. This discussion will pertain chiefly to the management of this unusual complication of pregnancy and include brief case reports of 5 patients whom I have had the opportunity of observing and operating upon during the past twenty years.

According to Bland and Montgomery, between 1813 and 1938, a total of 321 approximately full-term or at least viable secondary abdominal pregnancies were reported. Taking into consideration the number which undoubtedly have not been reported, this condition still remains one of the most uncommon complications of obstetric practice. It is generally conceded that the maternal mortality rate associated with this condition is between 30 and 40 per cent, with a fetal mortality rate of approximately 50 per cent. Even though the child does survive, Nature has done all within its power to destroy it by causing many deformities and abnormalities that make development of a normal human being practically impossible. *On the other hand*, a sufficient number of cases have been reported where the offspring has been normal, that should one encounter a patient where delay in operation might mean a viable child, it would seem advisable to defer the operation.

According to Bodenheimer, it is not always possible to make this very difficult diagnosis previous to operation. In a series of 236 cases that he studied, only 83 were diagnosed preoperatively.

Eminent medical authorities of this country agree that the management of the placenta is the most important phase of this condition. Practically all standard textbooks and other literature on the subject advise leaving a live placenta in situ unless it can be removed very easily. Schumann in his very excellent monograph on ectopic pregnancy, published in 1928, states that the placenta should be left in situ and if necessary, subsequently removed. He refers to Jewett's case, published in 1923, where the placenta was very large and firmly attached to the right side of the posterior surface of the uterus; the right broad ligament extending into the cul-de-sac and up the posterior pelvic wall as far as the brim of the pelvis, overlying the iliac vessels on that side. In this case the placenta was left in situ, the cord ligated and cut close to its insertion, and the patient made an uneventful recovery. He also states: "The tendency is steadily growing to regard the placenta as a digestible, autogenous tissue mass and to leave it undisturbed; the child and membranes, as well as any pathological pelvic organs being removed and the abdomen closed without drainage." In his recent textbook on obstetrics, he says that reports of recovery without difficulty make this procedure the best plan of treatment, but makes no statement as to the possibility of

*Read at a joint meeting of the New York, Philadelphia and Boston Obstetrical Societies, New York, April 9, 1940.

- (10) *Robinson, W. D., Melnick, D., and Fields, H., Jr.*: J. Clin. Investigation 19: 399, 1940. (11) *Harris, L. J., Leong, P. C., and Ungley, C. C.*: Lancet 234: 539, 1938. (12) *Peters, R. A.*: Lancet 1: 1161, 1936. (13) *Lohmann, K., and Schuster, P.*: Naturewissenschaften 25: 26, 1937. (14) *Weiss, S., and Wilkins, R. W.*: J. A. M. A. 109: 786, 1937. (15) *Booher, L. E., and Hartzler, E. R.*: U. S. Dept. Agriculture, Bulletin No. 707, December, 1939. (16) *Stiebeling, H. K., and Philipard, E. F.*: Circular No. 507, U. S. Dept. of Agriculture, Washington, January, 1939. (17) *McCance, R. A., Widdowson, E. M., and Vernon-Roe, C. M.*: J. Hyg. 38: 596, 1938. (18) *Jolliffe, N.*: Internat. Clin. 4: 46, 1938. (19) *Strauss, M. B.*: J. A. M. A. 110: 953, 1938. (20) *Boerma, N. J. A. F.*: Nederl. tijdschr. v. geneesk. 4402, 1931. (21) *Balfour and Tolpade*: Quoted by Guggisberg, Ber. ü. d. ges. Gynäk. u. Geburtsh. 37: 401, 1938. (22) *Fujita, Y.*: Jap. J. Obst. & Gynec. 17: 461, 1934. (23) *Andrews, V. L.*: Philippine J. Sc. 7: 67, 1912. (24) *Luikart, R.*: AM. J. OBST. & GYN. 25: 810, 1933. (25) *Plass, E. D., and Mengert, W. F.*: J. A. M. A. 101: 2020, 1933. (26) *Strauss, M. B., and McDonald, W. J.*: Ibid. 110: 1665, 1938. (27) *Hildebrandt, A., and Otto, H.*: Munchen. med. Wchnschr. 85: 1619, 1938. (28) *Sure, B.*: J. Nutrition 18: 187, 1939. (29) *Neuweiler, W.*: Arch. f. Gynäk. 169: 19, 1939. (30) *Elsom, K.*: J. Clin. Investigation 16: 463, 1937. (31) *Moore, C. U., and Brodie, J. L.*: Am. J. Dis. Child. 34: 53, 1927. (32) *Siddall, A. C.*: AM. J. OBST. & GYN. 35: 662, 1938. (33) *Yasunami, H.*: Jap. J. Obst. & Gynec. 21: 239, 1938. (34) *Ross, R. A., Perlzweig, W. A., Taylor, H. M., McBryde, A., Yates, A., and Kondritzer, A. A.*: AM. J. OBST. & GYN. 35: 626, 1938. (35) *Vignes, H.*: Maladies des Femmes Enceintes, Maladies de la Nutrition, Paris, 1935, Masson & Cie. (36) *Ueno, J.*: Jap. J. Obst. & Gynec. 17: 404, 1934. (37) *Shin, H.*: J. Chosen M. A. 23: 41, 1933. (38) *Stahler, F.*: Deutsche med. Wchnschr. 64: 1137, 1938. (39) *Dubrausky, V., and Lajos, A.*: Zentralbl. f. Gynäk. 63: 1069, 1939. (40) *Cowgill, G. R.*: The Vitamin B Requirement of Man, New Haven, Conn., 1934, Yale University Press. (41) *Rose, M. S.*: The Foundations of Nutrition, New York, 1933, The Macmillan Company. (42) *Daniel, E. P., and Munsell, H. E.*: U. S. Dept. of Agriculture, Publication No. 275, Washington, D. C., 1937. (43) *Cowgill, G. R.*: J. A. M. A. 113: 2146, 1939. (44) *Vorhaus, M. G., Williams, R. R., and Waterman, R. E.*: Ibid. 105: 1580, 1935. (45) Rep. on Physiological Bases of Nutrition, League of Nations Health Comm. Tech. Commission, London, 1935. (46) *Cowgill, G. R.*: Human Requirements for Vitamin B, The Vitamins, Chicago, 1939, p. 229. (47) *Dieckmann, W. J., and Swanson, W. W.*: AM. J. OBST. & GYN. 38: 523, 1939. (48) *Baker, A. Z., and Wright, M. D.*: Proc. Roy. Soc. Med. 29: 1145, 1936. (49) *Westenbrink, H. G. K., and Goudsmit, J.*: Arch. néerl. de physiol. 23: 79, 1938. (50) *Gaetgens, H. G.*: Grundlagen der Schwangerenernährung, Dresden and Leipzig, 1940, Theodor Steinkopff, p. 52. (51) *Bowes, A. DeP., and Church, C. F.*: Food Values of Portions Commonly Served, Philadelphia Child Health Society, Philadelphia, ed. 2, November, 1939. (52) *Weiss, S., and Wilkins, R. W.*: Ann. Int. Med. 11: 104, 1937.

Sezary, A.: The Local Treatment of Soft Chancre and Cutaneous Pyoderma by Sulfamide Powder, Presse Méd. 47: 1408, 1939.

The author quotes Lepinay's experience in the treatment of soft chancre and various pyodermas by the local application of the new para-amino-phenyl-sulfamide. Lepinay, treating 11 cases by dusting the powder upon soft chancres, obtained 10 cures. The one not responding appeared to be a case of mixed chancre. At the end of twenty-four hours, suppuration decreases considerably and may disappear, pain leaves, and the ulceration is halted. The second day the scarring begins. Healing is complete by the third to the eighth day.

The treatment is well tolerated. If the sulfamide powder is mixed with iodoform powder, it seems to give a double advantage, rapid healing ability with an absence of odor. With associated adenitis, Lepinay recommends sulfamide by mouth and vaccine therapy. If the lesions are old, the author recommends débridement to permit a local contact with the sulfamide powder. For those lesions involving the anus, sulfamide suppositories may be used.

Encouraged by his results from treating soft chancre with sulfamide, he used it also in several cases of pyoderma and cutaneous gangrene. He obtained rapid healing, followed by epidermatization, in these cases.

CLAIR E. FOLSOME.

I believe the following five case reports clearly illustrate the various complications which might be associated with this condition. The first four will be discussed very briefly and the fifth in more detail because of its rather unusual outcome.

CASE 1.—The patient was a para iv in whom the diagnosis of abdominal pregnancy was made in the seventh month of gestation. It was doubtful whether the child was alive. At operation it was found to be alive but did not survive. In extracting the fetus, part of the placental attachment was torn, and a profuse hemorrhage was controlled only by packing. The patient died three hours following operation from shock.

CASE 2.—The patient was a para iii. Diagnosis of abdominal pregnancy was made at six and one-half months and a live fetus was removed which did not survive. An attempt was made to remove the placenta but the resultant hemorrhage, which was controlled only by firmly packing the placental site, made this impossible. The patient reacted nicely from the operation. On the sixth and seventh days, the packing was gently loosened and on the eighth day it was removed without any apparent difficulty. A small pack was re-inserted and at the time this was removed there was no bleeding. One hour later, however, a severe secondary hemorrhage occurred which resulted in death before combative measures could be instituted.

CASE 3.—The patient, a para vii, was admitted to the hospital at the third month of gestation with a diagnosis of threatened abortion. There had been moderate bleeding and occasional cramplike pains in the lower abdomen. Bleeding ceased after rest in bed and sedation, and she was discharged from the hospital without a vaginal examination. This patient was not seen again until she was approximately six and one-half months pregnant, when she was admitted because of rather acute abdominal distress with slight bloody vaginal discharge. At that time, examination revealed the presence of a fetal head in the cul-de-sac and a uterus, the size of which was not commensurate with the estimated month of gestation. These findings were corroborated by x-ray which revealed the presence of two fetal skeletons. The patient stated she had not felt life for several weeks. Immediate operation was performed and the placenta was found lying on top of the uterus and coils of intestine. Both fetuses were behind the uterus and underneath the placenta. In order to remove them, some of the placental attachment had to be freed. Although life had not been felt by the patient for several weeks, profuse hemorrhage occurred when the placenta was detached. The fetuses were removed as quickly as possible and packing was inserted. The patient was returned to the ward in good condition and the packing was not disturbed for ten days, at the end of which time the patient was prepared as for any abdominal operation, taken to the operation room, and after the usual preparation, the packing was carefully and slowly removed. The patient was kept in the operating room for two hours following this procedure, and my assistants and I remained scrubbed. There was no secondary hemorrhage. A shorter pack was inserted and the patient was returned to the ward. The second pack was removed on the fourth day without serious bleeding. The resultant sinus drained for about three weeks and then closed spontaneously. Examination of this patient two years later showed her to be in good condition with no palpable pelvic mass.

CASE 4.—The patient, a nullipara, was seen in consultation in an up-state town when she was supposedly seven and one-half months pregnant. The diagnosis of abdominal pregnancy had been made by the family physician and fetal motion had ceased four weeks previously. The patient had been running a temperature of 101° F., in the evening, for two weeks before being seen by me. Because of probable post-operative complications, she was removed to Philadelphia by ambulance. After careful preparation, including blood typing, she was operated upon. Upon opening the peritoneal cavity a macerated fetus was found enclosed in a sac which had a very dirty, greenish yellowish appearance. There was no evidence of a placenta.

failure of absorption. Bland and Montgomery also advise this procedure but make the statement that the placenta may have to be removed at a later date.

It has been fairly well demonstrated, in the number of reported cases, that when this procedure of leaving the placenta in situ is carried out, recovery usually is rapid and uneventful. The older plan of marsupialization with moderate packing of the cavity with gauze has been frowned upon by many writers because of the prolonged convalescence and the possibility of sinus formation which might necessitate secondary operation for repair of the abdominal wall. Objection has been raised to leaving the placenta in situ and closing the abdomen without drainage because of the possible detachment with subsequent hemorrhage following operation. This, however, does not seem to occur. This procedure is followed in those cases where the placenta is still alive. When operating upon a patient where the fetus has been dead for some time, there is usually no difficulty in removing most of the placenta and the membranes along with the fetus. This, however, is not constant, as in one of the cases I am reporting, although the fetus had been dead for some time the placenta was still highly vascular and as a result profuse hemorrhage occurred. Recently Nicodemus observed a patient in whom the placenta did not absorb, necessitating drainage of the resultant abscess and removal of the remaining portion of the placenta. And still more recently I have encountered a case in which a second operation for removal of the placenta became necessary. Because of Nicodemus' report and the one I am now making, it seems necessary to call attention to the fact that absorption does not always take place. In the case reported by Nicodemus, the diagnosis was not made prior to operation, and there had been ineffectual attempts at induction of labor from below before the abdomen was opened. The inability to induce labor and a progressive pre-eclamptic toxemia were responsible for the decision to deliver by abdominal section. A live child was obtained. The patient returned to the hospital in two months with elevation of temperature, leucocytosis, and other signs of infection. Secondary operation for drainage of the resultant abscess formation resulted in the ultimate recovery of the patient. Nicodemus stated in his case report that a search of the literature failed to reveal a similar case in the last decade.

As this feature of the management of this complication is not stressed, it seems feasible to review the management of this condition. Furthermore, any condition which has a maternal mortality rate of from 30 to 40 per cent should be considered a possible virgin field for improvement of our already supposedly too high maternal mortality. Although the subject is discussed satisfactorily in the more recent textbooks, it has occurred to me that information necessary for the guidance of the occasional operator, or one who has not encountered this complication previously, could be clarified.

It is not my purpose to formulate any strict rules to govern the management of secondary abdominal pregnancy, but rather to mention a few safeguards which might lead to a decrease in our mortality rate. Nor is it my desire to criticize what is written in the more recent textbooks but rather to elaborate upon what has already been said.

negative. Within a week the mass had increased a trifle in size and she had experienced two other attacks of nausea and vomiting together with difficulty in proper elimination. She was afebrile, had a normal sedimentation rate, and normal leucocyte count. Because of the increase in size of the mass and because of questionable partial intestinal obstruction, it was decided to reopen the abdomen. This was done on March 6, two months after the original operation. The abdomen was opened through the old incision, and upon incising the peritoneum a large mass was found originating in the right side, looking not unlike an ovarian cyst. It was completely encapsulated and was adherent on all surfaces. Adhesions to the parietal peritoneum were freed without difficulty and gave rise to no bleeding. On continuing to break up the adhesions it was found that posteriorly several sections of intestines and the posterior peritoneum were so firmly united with the sac that to continue attempting this procedure would have resulted in disaster. By this time, however, the encysted mass could be brought well up into the abdominal incision. It was incised and a large basinful of necrotic placental tissue weighing 660 Gm., together with organized blood clot, was removed. There was no fresh bleeding. Evidently the increase in size had been due to hemorrhage into the cyst cavity. Microscopic examination of the tissue removed proved it to be definitely placental tissue. The sac was then cut off down to the portion where it was densely adherent and the edges sewed to the parietal peritoneum. A small pack was inserted into the cyst cavity and the usual closure of the abdomen completed the operation. The patient reacted very well. Starting on the third day, a small amount of packing was removed each day until it was entirely out on the seventh day. Her convalescence was uneventful and she was discharged from the hospital on the fourteenth day in good condition with the wound entirely healed. The discharge from the sac cavity at no time was purulent in character. Up to the present time the patient has continued to be in good health and the baby now weighs over 7 pounds.

In reviewing these summaries I would like to point out some pertinent facts as to the good or bad judgment exercised in the management of these five cases.

In the first case, the removal of the child was not accomplished with sufficient care so as not to disturb the placenta, and fatal hemorrhage resulted. Also, prompt combative measures were not in readiness to control shock from hemorrhage.

In the second case, the hemorrhage was unavoidable, but sufficient safeguards were not on hand at the time of removal of the packing.

In the third case, unavoidable hemorrhage occurred but proper blood transfusion and care at the time of operation, together with proper safeguards at the time of removal of the packing, resulted in recovery of the patient.

In the fourth case, where the child was known to be dead, all precautions were taken at the time of operation and fortunately no hemorrhage was encountered. No effort was made to remove the sac, because it was thought to be walled off from the other viscera and was potentially infected. I believe that an attempt to do so would have resulted in peritonitis.

The successful outcome of the fifth case, was due to the careful study of the patient's general condition, proper blood typing prior to operation, good judgment in deciding when to operate and where to make the incision so as to avoid the placenta, and the great care exercised in inspecting the placental site. At the second operation, I believe the

The sac seemed to be entirely walled off from the rest of the peritoneal cavity, and as the incision was made directly over the sac, none of the other abdominal viscera were seen. The macerated fetus was removed, but because of evident infection no attempt was made to remove the sac, which was marsupialized and drained. The drainage was very markedly purulent. No bleeding occurred, and the patient, after draining rather profusely for two or three weeks, made an uneventful recovery. Unfortunately, this patient died four months following operation of miliary tuberculosis, but up to that time she had had no abdominal symptoms.

CASE 5.—The patient, a para ii, 38 years of age, who had not been pregnant for nineteen years, was admitted to my service at the Philadelphia Lying-in Hospital on Jan. 1, 1940, with Jan. 26, 1940 as the expected date of confinement. Her family physician informed us that he had been in attendance on her for forty-eight hours prior to admission, during which time she had been in more or less constant labor, but according to his findings, had made no progress. On abdominal examination the child could be felt very distinctly and the heart sounds were auscultated in the lower left quadrant. A large, doughy mass could be palpated on the right side, but the fundus of the uterus could not be felt. Vaginal examination revealed the fetal skull to be in the left vaginal vault. The sutures and fontanels were easily outlined. The cervix was displaced to the lower right angle of the vagina, was soft, but not effaced nor dilated. On bimanual examination the uterine contour could not be outlined. A diagnosis was made of spurious labor and an abdominal pregnancy with a living child. As the patient had not been under our supervision and because she had had no rest for forty-eight hours, immediate operation was deemed inadvisable. This in spite of the fact that the usual history of these patients is that following attempts at labor the fetus usually dies. She was given morphine which enabled her to get much needed rest. In the meantime, routine studies were carried out. X-ray did not corroborate our diagnosis. The blood Wassermann was found to be positive, while other studies were essentially negative. In view of the fact that the child was living and the patient's general condition much improved, decision to operate was made on January 6. Before proceeding, however, the patient was typed and the necessary blood was obtained and in readiness in the operating room. The fetus seemed to be lying entirely on the left side, and because of our experience in previous cases, the abdomen was opened through a left rectus incision. Upon opening the peritoneum about 30 c.c. of blood and clots was found in the peritoneal cavity. There was no evidence of an amniotic sac. The fetus was lying on top of the intestines. A female child, weighing 4 pounds 13¾ ounces, was removed; she appeared to be in good condition and cried immediately. The placental site was then very carefully and gently inspected in order to avoid hemorrhage. It was found that the placenta was attached, starting at the right cornu of the uterus and extending upward on the right side to about the level of the umbilicus. It was not only attached to the lateral pelvic wall but the intestines were also involved. The cord was then ligated and cut close to its placental attachment. The loss of blood was minimal and the abdomen was closed without drainage. Patient's convalescence was uneventful. The highest elevation of temperature occurred on the second day postoperatively when it reached 100° F. The patient was kept in the hospital three and one-half weeks, during which time she had no unusual symptoms. At the time of discharge from the hospital there was a distinct fullness in the lower right part of the abdomen and a mass about the size of a small grapefruit could be palpated. This patient insisted upon going home and as her temperature was normal and she had no complaints, she was permitted to do so. Three weeks later she returned complaining of abdominal pain, particularly in the right side of the abdomen, associated with nausea and vomiting and more or less obstinate constipation. She had had some vaginal bleeding and one attack of persistent vomiting. At this time there was a large, well-defined mass in the lower abdomen, approximately the size of a four months' gestation. She was readmitted and kept under observation. Her Friedman test was returned positive, but a second Friedman done in dilution proved to be

Ninth, When hemorrhage is encountered and packing is necessary, removal of this packing, after it has been loosened on several successive days, should be attempted only after careful preparation has been made for further transfusion and reopening of the abdomen.

Tenth, Where the placenta is alive and a living child removed, no attempt at separation or removal of the placenta should be made. The abdomen should be closed without drainage.

Eleventh, In view of our recent experience, the placenta does not always resorb and as in Nicodemus' case, may even result in abscess formation. When the former occurs, removal of the placenta should be deferred for two months, unless there is evidence of abscess formation, or as Adair points out, intestinal obstruction, at which time immediate operation is indicated. If secondary removal becomes necessary and the entire sac wall cannot be removed, marsupialization with packing of the cavity seems to be indicated.

In drawing up the aforementioned conclusions, I have endeavored to show the dilemmas into which we were placed in managing these five cases and trust that I have adequately stressed the importance of properly safeguarding the patient against tragic complications by making a proper diagnosis, fortifying the patient against shock, operating at the proper time, and in the proper surroundings where adequate equipment and medication are available to combat shock, if it should occur; and last, but not least, using proper judgment and technique with regard to the placenta.

REFERENCES

Bland, P. Brooke, and Montgomery, Thaddeus L.: Practical Obstetrics, third revised edition, 1939, p. 345. Schumann, Edward A.: Extra-Uterine Pregnancy, Gynecological and Obstetrical Monographs (Cumulative Supplement and Composite Index), 1928, p. 216. Schumann, Edward A.: A Textbook of Obstetrics, Philadelphia, 1936, W. B. Saunders Co., p. 345. Nicodemus, R. E., and Carrigg, L. G.: AM. J. OBST. & GYN. 39: 153, 1940. Adair, Fred L.: Obstetrics and Gynecology, 1940, vol. 1, p. 700.

807 SPRUCE STREET

DISCUSSION

DR. CARL H. DAVIS.—Last year a colored girl, on my service at Delaware Hospital had a secondary abdominal pregnancy that followed rupture of the right tube. The technique described by Dr. Lull was followed, namely, that of removing the macerated fetus and not attempting to remove the placenta. The patient made an uneventful recovery and has had no trouble since then.

One point in treatment should be emphasized, and that is the necessity of having blood available for these patients and for all patients who are admitted to a hospital with bleeding during pregnancy. Each year many women lose their lives because an effort has not been made to secure immediate typing of blood and prompt transfusion when it is needed.

DR. WILHELM LATZKO.—Dr. Lull remarked that the great majority of abdominal pregnancies are based upon the secondary implantation of an ovum separated from its original attachment in the genitals by rupture or expulsion. This widespread conception assumes that the ovum can travel through the peritoneal cavity and survive until the chorionic villi have created a new connection with the maternal tissue. This assumption is, a priori, unbelievable. Moreover, it is not supported by any clinical or embryologic observation.

incision and removal of the encysted placenta without attempting to remove the entire sac, had a definite bearing on the patient's ultimate recovery.

From my experience in observing these five cases, together with what I can gather from the most modern textbooks and recent literature on the subject, I would like to offer the following conclusions:

First, In the management of advanced ectopic pregnancy or so-called secondary abdominal pregnancy, there can be no absolute rule as to procedure. However, certain general principles should be followed. In other words, each patient must be individualized.

Second, The advisability of delaying operation with the idea of obtaining a living child is questionable, inasmuch as many of these children have congenital abnormalities and the risk to the mother in deferring operation seems to be greatly increased. When the diagnosis is made late in pregnancy, waiting a week or two seems advisable but operation should be performed between the thirty-sixth and the thirty-eighth weeks. Permitting the patient to advance to full term increases the maternal risk and decreases the chances of having a living offspring.

Third, If death of the fetus occurs, it seems advisable to defer operation for three or four weeks until the vascularity of the placenta has been markedly decreased and a partial separation has taken place. During the waiting period the patient should be kept in the hospital under close observation for hemorrhage and infection of the gestational sac. If the fetus has been known to be dead for several weeks, immediate operation is indicated.

Fourth, Careful preparation for combating possible hemorrhage should be made before operation is attempted. The patient's blood should be typed and the necessary blood at hand, so that, if necessary, it can be given immediately.

Fifth, Incision of the abdominal wall should be made over the site of the child rather than over the placenta. This of course is not always possible, but as demonstrated in Case 5, can sometimes be done.

Sixth, Careful removal of the child without disturbing the placental site is important. This is not always possible, however, as demonstrated in Case 3. When it is seen that the placenta will be partially detached in removing the fetus, the larger vessels should be ligated before attempt at separation is made.

Seventh, When operating upon a patient where the fetus has been known to be dead for some time, the fact that removal of the placenta may still give rise to serious hemorrhage must not be lost sight of, and although removal can usually be accomplished, it is necessary in some instances to resort to packing to control the bleeding. It seems advisable not to disturb the packing for at least ten days.

Eighth, In operating upon a patient where the fetus has been dead for some time and there is evidence of infection, approach to the sac should be made with care and if possible, extraperitoneally. These cases should always be drained and removal of the sac should never be attempted.

DR. LULL (closing).—Dr. Latzko may be correct in his feeling as to the existence of primary abdominal pregnancy. The authorities, however, in this country do not believe that it occurs and I have abided by their writings rather than my own opinion.

It is possible as Dr. Cosgrove suggests that I stress too much the point that the placenta does not always resorb. I did this because there is nothing in the literature that I can find on that aspect of the subject. I have endeavored, however, to impress the fact that the proper management of the live placenta is to let it alone. There is no question of this in my mind in spite of the fact that this one case gave rise to partial intestinal obstruction.

Dr. Studdiford brought up the very important question as to how long it takes the placenta to become absorbed. I am sure I would not have operated upon the last patient at the end of two months if she had not had the symptoms that she had and if the mass had not been increased in size.

PREGNANEDIOL DETERMINATION AS AN AID IN CLINICAL DIAGNOSIS*

C. L. BUXTON, M.D., NEW YORK, N. Y.

(From the Department of Anatomy and the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

THE determination of the metabolism and excretion of progesterone, the corpus luteum hormone, has heretofore been impossible because there has been no accurate method for measurement of this substance either in the body or as an excretion product. Only small amounts of progesterone have been found in human urine or placenta¹ and from even as much as 50 Gm. of human corpora lutea only questionable amounts of progesterone have been obtained.² Five hundred cubic centimeters of blood from a pregnant woman has yielded negative results when tested by bio-assay methods.³

The discovery of pregnanediol, however, and its identification as an excretion product of progesterone has now enabled us to determine the presence of progestational activity with a fair degree of accuracy. Pregnanediol is found in the urine during the time and only during the time when the corpus luteum is generally considered to be active, i.e., during pregnancy and during the latter half of the menstrual cycle. It is excreted in the urine as sodium pregnanediol glucuronidate and in this form may be quantitatively measured according to a chemical method developed by Venning.⁴

METABOLISM AND EXCRETION

The metabolism of progesterone to sodium pregnanediol glucuronidate in the body is a complex procedure. The glucuronic acid complex is probably conjugated in the liver⁵ and the whole compound is presumably excreted by the kidney, although no work has as yet been done to determine its presence in feces. Any abnormality in these structures causing inefficient metabolism or excretion may well result in a diminished or negative finding in the urine. It is possible also

*Aided by grants from the Rockefeller Foundation, administered by Dr. P. E. Smith, and from the National Committee on Maternal Health to Dr. B. P. Watson.

The progesterone used in this study was furnished by Hoffmann-LaRoche Company, through the courtesy of Dr. Shäner, and by the Schering Corporation, through the courtesy of Dr. Stoner.

Only two reports of such an occurrence are to be considered. Micholitsch in a case of fimbrial pregnancy found a placental polypus as an apparent remnant of the original implantation of the fecundated ovum in the Fallopian tube. Wallace, who had operated upon a patient with myoma complicated by tubal pregnancy, implanted the enucleated ovum in the bed of the likewise enucleated myoma and later observed the birth of a normal child at term. Both these cases could be interpreted as twin pregnancies.

On the other hand, the primary implantation of a fecundated ovum on the peritoneum is quite comprehensible as we know, from our investigations upon endometrioma, that the celom includes areas of cells not fully differentiated or else differentiated in the direction of endometrial tissue. That these areas are qualified for the primary implantation of a fecundated ovum is not only believable, but proved. I mention the communications of Dawson, Vara, Vozza, Frankel and Schenck, and myself.

In conclusion, I wish to point out that except for those cases where the placenta is retained in the reproductive tract while the fetus escapes into the abdominal cavity and continues there its life, there exists no real secondary abdominal pregnancy. All abdominal pregnancies in which the placenta or chorial villus is in intimate connection with the peritoneum are primary.

DR. ALFRED C. BECK.—The method of leaving the placenta in the abdomen without drainage was recommended by me in a paper which I read before the American Medical Association in 1918. This recommendation resulted from my experience with a full-term extrauterine pregnancy in which I attempted to remove the placenta and thereby started an alarming hemorrhage. The child not only survived but reached 22 years of age this year, and last month gave birth to a normal infant in the Long Island College Hospital. At that time, it also was my good fortune to see the grandmother who had the abdominal pregnancy twenty-two years ago.

DR. WILLIAM A. JEWETT.—The case of mine to which Dr. Lull has referred was kept under observation for many months following the operation, and the placental mass was found to decrease in size very slowly. It was palpable two years later on bimanual examination. Two and a half years after the operation for abdominal pregnancy I operated upon her for appendicitis and at that time examined the right adnexa, the site of the original implantation. I found a mass that was grossly similar to that of a chronic inflammatory disease. I removed this mass and had careful sections made for microscopic study but no evidence of placental tissue was to be found in the material.

DR. SAMUEL A. COSGROVE.—Dr. Lull has said that he hopes his experience will be a guide to the occasional operator. He has mentioned, however, the point that secundines left in the abdomen may not always resorb, and may become a source of subsequent trouble. With reference to the occasional operator, however, it should be emphasized that while different circumstances may indicate different types of management, the most desirable procedure in general is the closure of the abdomen without disturbing the placenta.

DR. WILLIAM E. STUDDIFORD.—I have seen one case which may be of interest in connection with the rate of absorption of the placenta in abdominal pregnancies, a patient who was operated upon at Bellevue Hospital in March, 1939. She had an abdominal pregnancy, the placenta being situated in a very fortunate position for follow-up. It covered the entire posterior portion of the pelvic peritoneum and the cul-de-sac. When the fetus was removed, the placenta was unavoidably disturbed, and profuse bleeding resulted, necessitating packing. The packing was removed without the disastrous consequences which Dr. Lull mentioned. This patient has been followed in the clinic ever since discharge in an effort to discover how long it took for the placenta to become absorbed. She was last seen in the clinic in January, I think, and a mass can still be felt in the cul-de-sac, although she has no symptoms whatsoever from its presence.

Although there are great variations in the quantitative excretion of sodium pregnanediol glucuronidate during pregnancy, the mean of daily excretions follows a definite curve.

Venning and Browne¹³ followed nine pregnant patients daily throughout their period of gravidity and found values of from 4 to 10 mg. up to the sixtieth day of pregnancy. A rise then occurred, reaching a level of about 40 mg. at six months and a peak of 75 to 80 mg. in the eighth month.

Weil¹⁴ observed that values were considerably lower than this in patients with toxemia of pregnancy, a finding confirmed by Browne and Venning.¹³ It has been the common experience of workers with this material, however, that urine from toxemia patients emulsifies so extensively during the butyl alcohol extraction that it is difficult to keep from losing a certain amount of the substance. Also, it may be possible that, with the extensive water retention and decreased excretion of urine during toxemia, pregnanediol is withheld in the tissues.

No pregnancy cases have been observed here or reported elsewhere, which have had negative pregnanediol determinations. Consequently, so far as is known at present, a negative diagnosis of pregnancy may be considered very accurate by this method. In several hospital cases where the diagnosis of pregnancy was doubtful, this test has helped materially in reaching a definite conclusion. The two cases listed below are examples.

J. H., aged 27 years, a patient with a history of severe toxemia of pregnancy, had previously delivered a macerated fetus and had had a therapeutic abortion done because of toxemia. At the time of admission to the hospital on March 29 she gave a history of menstruating last on February 6. Because of history of previous severe toxemia, therapeutic abortion was decided upon. She bled a little on the evening of March 29, however, and a question arose as to a definite diagnosis. Urine was taken for both Aschheim-Zondek test and pregnanediol determination on April 1. The Aschheim-Zondek test was positive but no sodium pregnanediol glucuronidate was found in the urine. However, since the Aschheim-Zondek test was positive, a laparotomy for termination and sterilization was decided upon. There was no evidence of pregnancy. In this case there apparently had been a spontaneous abortion the night of admission to the hospital. Very possibly pregnanediol disappears from the urine following the termination of pregnancy more quickly than does the prolan searched for in the Aschheim-Zondek test.

Another patient, E. H., aged 27 years, had had four previous miscarriages. When she was about three and one-half months pregnant, a pregnanediol determination was done because she had had occasional periods of spotting and a question arose as to the possibility of there being an inherent corpus luteum deficiency. No pregnanediol was found in the urine and examination disclosed that the patient was not pregnant. She had either never been pregnant or had aborted. No thorough pelvic examination had been done previously for fear that manipulation might start further bleeding. As a matter of fact, a careful investigation of this patient's past history disclosed no proof that she ever had been pregnant, either on this occasion or the previous ones, and this case cannot actually be considered one of repeated abortion.

On the other hand, the positive diagnosis of pregnancy from pregnanediol content in the urine is not so easily determinable. Wilson, Randall and Osterberg¹⁶ consider the finding of 10 mg. or more of pregnanediol in the urine following a missed period diagnostic of pregnancy, and a smaller amount in a patient with previously regular periods highly suspicious. The fact that a patient may, however, be having a delayed menstrual period must be considered.

that progesterone may break down into other excretion products similar to pregnanediol, such as pregnanolone or allopregnanediol.⁶ Heretofore it has been thought that the uterus was a necessary adjunct to this metabolic process. Browne and Venning⁷ observed that progesterone injected into a hysterectomized woman was not excreted as pregnanediol. Hamblen and others⁸ also observed this to be the case and further found that if a curettage were done during the luteal phase of the cycle, pregnanediol, which was present before, disappeared. He draws the conclusion from this procedure that endometrium is necessary to metabolize the product.

In this laboratory pregnanediol determinations were done on four women during and following the injection of 30 mg. of progesterone daily for three days. Three of these patients had had subtotal and one had had a total hysterectomy. Two of these patients excreted sodium pregnanediol glucuronide, as shown in Table I, whereas the other two had no excretion.

TABLE I

PATIENT	AGE	OPERATION	PROGESTERONE GIVEN	DAY GIVEN	PREGNANEDIOL FOUND
V. C.	49	Total hysterectomy Bilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	
				2	0
				3	0
				4	3.7 mg.
				5	0
G. T.	40	Subtotal hysterectomy and bilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	0
				2	0
				3	0
I. S.	32	Subtotal hysterectomy and unilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	
				2	0
				3	1.9 mg.
				4	1.3 mg.
				5	1.7 mg.
M. N.	38	Supravaginal hysterectomy and bilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	0
				2	0
				3	0

Furthermore, Buxton and Westphal⁹ have found that men receiving injections of progesterone excrete large amount of sodium pregnanediol glucuronide. The uterus, therefore, is not considered a necessary adjunct to this metabolic process.

Since the metabolism of progesterone apparently involves a number of factors, an investigation was made of various laboratory animals in which it might be possible to study further the process. It was found that rabbits and cats excreted no pregnanediol either in their normal state or during pregnancy, and that monkeys excreted no pregnanediol even after injections of large amounts of progesterone.¹⁰ Hartman and Marker¹¹ observed that no pregnanediol was excreted in the urine of pregnant monkeys.

EXCRETION IN PREGNANCY

The greatest yield and the purest form of pregnanediol is excreted during pregnancy in the human being. Since the excretion of this substance continues even after the removal during pregnancy of the ovary¹² containing the corpus luteum, it is surmised that the product is probably elaborated by the placenta.

in three weeks, two determinations showed from 3 to 4 mg. of pregnanediol to be present, an amount which would be found in a castrate following injection of this amount of progesterone. In other words, this woman was apparently producing no progesterone, either from the corpus luteum or the placenta, or if she was, it was not being excreted as pregnanediol glucuronide. Also large amounts of artificially supplied progesterone were insufficient to maintain pregnancy. It is therefore assumed that some pathology was present in the placenta which not only prevented the production of progesterone but also prevented adequate nidation or nutrition of the trophoblast. The assumption may also be made that, if progesterone was being supplied, its utilization was in some way being prevented.

Repeated pregnanediol determinations in cases of threatened or habitual abortion may, therefore, give us a fairly definite indication as to whether or not the patient will continue with the pregnancy investi-

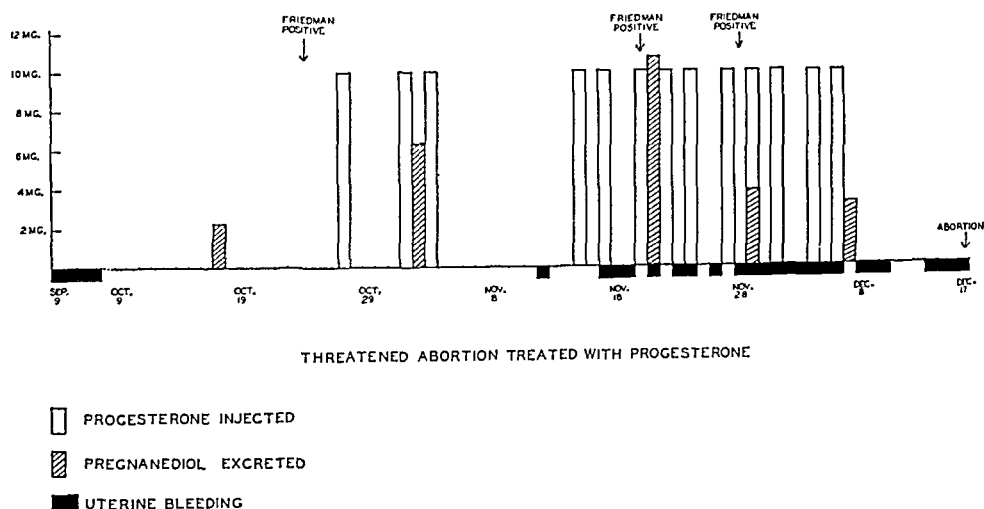


Fig. 1.

gated. They also give us some indication as to whether or not progesterone administration is being utilized by the organism. In the case presented above, the administered progesterone was apparently not being utilized and consequently its administration as a therapeutic agent was of no value.

EXCRETION IN NORMAL WOMEN

In the normal nonpregnant woman the excretion of sodium pregnanediol glucuronide has been found by us to occur only during the latter half of the menstrual cycle. It must be said, however, that the great majority of assays have been done only on the urine of the latter half of the menstrual cycle. Those done during the first half of the cycle have been incidental and consist of 11 determinations only, but none has contained sodium pregnanediol glucuronide.

Venning and Browne⁷ studied the excretion of 10 patients through one or more cycles. So far as was possible, they determined the occurrence of ovulation by means of ovulation pain, intermenstrual bleeding, and the occurrence of gonadotropic hormone in the urine, all of which are probably inaccurate. They found pregnanediol present twenty-four to forty-eight hours after these various "signs" of ovulation, although this was not always the case. Its excretion in-

Such a case is A. B., aged 40 years. Her last menstrual period was Dec. 7, 1938. She had slight bleeding in February and in March came to the clinic complaining of amenorrhea, nausea, and vomiting. Physical examination disclosed a number of fibroids increasing her uterus to the size of a four months' pregnancy. Her Aschheim-Zondek test was negative. Pregnanediol determination was 3.5 mg. She was operated upon for removal of the fibroids and the endometrium was found in the secretory phase with no evidence of decidua or trophoblast. This woman was probably undergoing the menopause and had one episode of delayed ovulation and menstruation. From this instance it will be seen that the presence of amenorrhea and pregnanediol simultaneously is not diagnostic of pregnancy.

Twenty pregnanediol determinations have been made in correlation with Aschheim-Zondek or Friedman tests in cases of suspected pregnancy in order to determine the accuracy of the two methods. Ten of these patients were proved to be pregnant by confirmatory findings in both Aschheim-Zondek and pregnanediol determinations, varying amounts of the latter being found in all cases, whereas in the ten cases with negative Aschheim-Zondek findings, no pregnanediol was present in the urine.

EXCRETION IN CASES OF HABITUAL ABORTION

Progesterone has been extensively used in the treatment of habitual abortion, on the theory that the cause of habitual abortion is insufficient progestational activity.¹⁷⁻¹⁹ Since heretofore there has been no method of measuring progestational activity, the treatment of these cases with progesterone has been theoretical.

It was therefore thought advisable to carry out pregnanediol determinations during early pregnancy on several patients with a history of three or more previous spontaneous abortions. Careful investigation of many of these cases revealed that the great majority of patients had only an indefinite history of abortion. There was no definite proof of pregnancy and the periods of amenorrhea which made the diagnosis of pregnancy probable were usually of only two to three weeks' duration. There were rarely a curettage and pathologic examination of the specimen.

Five patients in whom there was an accurate history of three or more spontaneous abortions were studied during early subsequent pregnancy, and they all excreted pregnanediol commensurate with normal amounts for their period of gravidity. One of these patients subsequently aborted again, however, and her history is given below.

B. P., aged 37 years, married twelve years with past obstetric history as follows: July, 1928, spontaneous abortion, three months; December, 1931, spontaneous miscarriage, six months; September, 1933, spontaneous abortion, three months; March, 1937, spontaneous miscarriage, five months; July, 1939, spontaneous abortion (Friedman positive), six weeks. The patient's past medical history, physical examination, and laboratory findings were essentially negative. The basal metabolic rate was -8; the Wassermann negative.

She had a normal period on September 9, did not menstruate in October and on October 20 her Friedman test was positive. Her further history is represented graphically in Fig. 1.

It will be observed that even unusually large amounts of progesterone did not maintain an adequate progestational activity as measured by pregnanediol excretion, and she aborted spontaneously in the third month of her pregnancy. After injection of over 100 mg. of progesterone

This is probably the case under normal conditions, but it is possible that corpus luteum formation may occur without extrusion of the ovum. The presence of an ovum trapped within the interstices of the corpus luteum has been observed in monkeys²³ and therefore this may possibly occur in the human being. Consequently, evidence of corpus luteum activity in the form of secretory endometrium or pregnanediol content of the urine is only *prima facie* evidence that ovulation has occurred. It is mainly evidence that there is corpus luteum activity present. It may be presumed that ovulation has occurred, and because corpus luteum formation after ovulation is probably the usual sequence of events, the presumption is quite valid.

In order to correlate the presence of pregnanediol in the urine with evidence of luteal change in the endometrium, Wilson, Randall and Osterberg,¹⁶ at the Mayo Clinic, obtained coincidental pregnanediol determinations and endometrial biopsies on 50 patients complaining of various gynecologic conditions. No pregnanediol in significant amounts was found in their cases in which specimens were taken during the proliferative phase of the cycle. Two cases were reported which did have less than 2 mg. present. No melting points were given for these determinations, a procedure which should be routinely followed, due to the many possible errors in the extraction process. Consequently, the significance of these two cases is doubtful. Of the determinations done at the time the endometrium, as shown by biopsy, was in the early or late differentiative, or secretory phase, there were many which contained no pregnanediol. This finding has also been observed by us, and will be discussed later.

Seventy-eight pregnanediol determinations were done in this laboratory on patients who at the same time were subjected to endometrial biopsy or operation for various causes, most of the biopsies having been taken in the sterility clinic. Of these 78 combined determinations, 65 have sufficient records so that the time of their next menstrual period may be accurately determined. All of these biopsies except two were taken during the last two weeks of the menstrual cycle.

Forty-five of these biopsies showed secretory endometrium. Urine determination for pregnanediol done at the same time or within a day or two of biopsy showed that 31 of the 45 had pregnanediol present in varying amounts, the smallest being 1.1 mg., the largest being 10.2. Of the 14 which had no pregnanediol present, 12 determinations were made within two days of menstruation, when none would be expected normally, 2 were done at times in the cycle when pregnanediol should be present. This finding will be discussed later.

Fifteen of the biopsies showed proliferative endometrium, all except two having been taken during the latter half of the cycle. No pregnanediol was found on coincidental urine determinations.

Five biopsies had questionable diagnoses and no definite decision could be made as to whether these were definitely proliferative or secretory. Coincidental urine determinations showed 0 pregnanediol in 3 cases, 2.7 mg. in one, and 4 mg. in one.

The absence of pregnanediol in the urine during the latter half of the cycle when secretory endometrium is present may be explained in several ways. In the first place, as has been stated previously, the substance disappears from the urine one or two days before menstruation under normal conditions, so that within this time limit pregnanediol absence in the presence of secretory endometrium may be considered physiologic. Also, in doing daily determinations on normal women it has been shown, as previously stated, that occasionally they skip a day

creased until about one week before menstruation, then fell off toward the end of the cycle and stopped abruptly, menstruation ensuing one to three days after the disappearance of pregnanediol. Although they found great variation in corpus luteum activity as measured by total pregnanediol excretion in one period, the total amount varying from 3 to 54 mg., they maintained that once the product was found, excretion continued without interruption until it stopped before the period. Pratt and Stover²¹ also found this to be the case, but this has not been the experience in our cases or in the series published by Hamblen and others.⁸

In doing random pregnanediol determinations during the last two weeks of the menstrual cycle on patients with regular menstrual periods, it was observed that occasionally no pregnanediol was found. Consequently daily determinations were done on three supposedly normal women. One of these women excreted no pregnanediol at any time during the two weeks before one period. The other two excreted amounts varying from 2.2 mg. to 7.5 mg. but there were occasional days during the period of excretion when they excreted none. A graphic representation of their excretion is shown in Fig. 2.

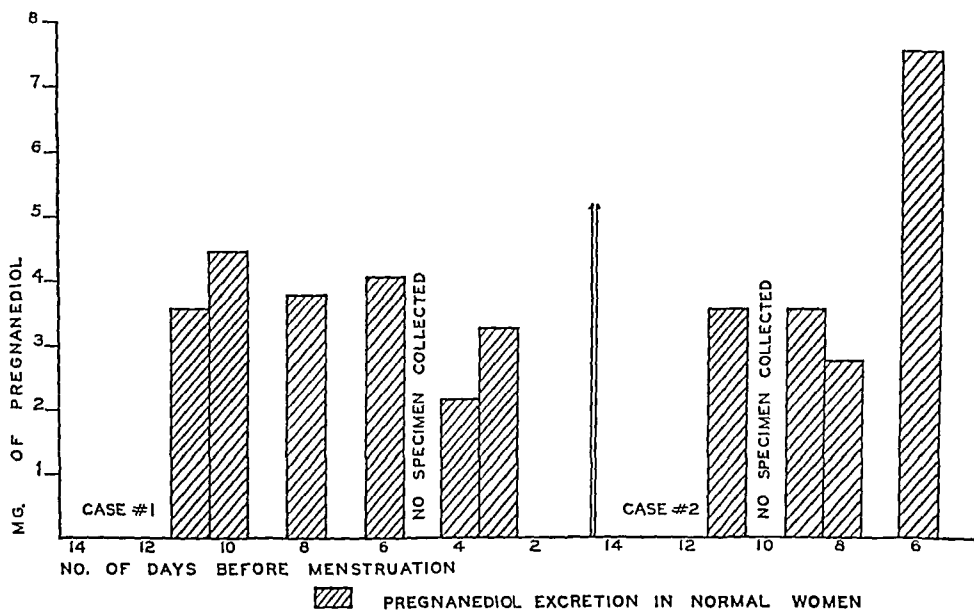


Fig. 2.

It will be observed that the amount of excretion varies considerably from day to day and according to no particular rule, but that there have been no instances of more than a one-day lapse during the period of excretion. Whereas in our procedures twenty-four-hour specimens were tested, Browne and Venning took forty-eight-hour samples, which may explain the discrepancy in results. This is an important differentiation, because, if it is true that a patient may normally skip a day during a normal period of excretion, one twenty-four-hour specimen taken as a diagnostic test of corpus luteum activity may not necessarily be accurate.

CORRELATION OF PREGNANEDIOL EXCRETION WITH ENDOMETRIAL BIOPSY FINDINGS

It has been generally considered heretofore that the presence of corpus luteum activity presupposes the phenomenon of ovulation.²²

Unfortunately, therefore, conclusions drawn from the interpretation of differences in the *quantitative* excretion of pregnanediol are undependable.

SUMMARY

1. Pregnanediol is defined as an excretion product of the corpus luteum hormone progesterone.

2. Its synthesis as sodium pregnanediol glucuronidate probably occurs in the liver. Its metabolism and excretion are not dependent upon the uterus or ovaries, as is shown by injection experiments on men and hysterectomized women.

3. The urine of monkeys, cats, and rabbits does not contain pregnanediol either normally, during pregnancy or after progesterone injections.

4. The greatest yield and purest form of pregnanediol glucuronidate occurs in the urine of pregnancy. No pregnant patients have been observed who do not excrete pregnanediol glucuronidate. Therefore the negative diagnosis of pregnancy may be made as a result of negative pregnanediol determination.

Pregnanediol is present in small amounts in the urine during the latter half of the menstrual cycle in normal women. Although the excretion during pregnancy is greater than that during the luteal phase of the menstrual cycle, a diagnosis of pregnancy cannot be made on this basis because the quantitative determination is not sufficiently accurate.

5. Five cases of habitual abortion were tested for pregnanediol excretion during subsequent pregnancies. One of these patients aborted spontaneously during the course of progesterone therapy. She showed unusually low pregnanediol excretion.

6. Seventy-eight simultaneous pregnanediol determinations and endometrial biopsies were done on patients, most of whom were in the sterility clinic. These tests were done in order to ascertain the accuracy of these two methods of determining progestational activity. It is apparent that pregnanediol is excreted during the time that the endometrium is being activated to a secretory phase and only during that time.

7. There are so many factors controlling the excretion of pregnanediol glucuronidate that the quantitative result is liable to variation. Therefore diagnosis cannot be made on a basis of *quantitative* differences in excretion.

I wish to express my gratitude to Dr. B. P. Watson, Chief of the Sloane Hospital for Women, and to Dr. Earl T. Engle, Department of Anatomy, College of Physicians and Surgeons, Columbia University, for their helpful advice and suggestions during the course of this study.

REFERENCES

- (1) Adler, A. H., de Fremery, P., and Tausk, M.: *Nature* 133: 293, 1934; Ehrhardt, K.: *München. med. Wehnschr.* 81: 869, 1934. (2) Claiberg, C. H., Thiel, W., and Ziecker, R.: *Arch. f. Gynäk.* 152: 61, 1932. (3) Bloch, P. W.: *Endocrinology* 20: 307, 1936. (4) Venning, E. H.: *Jour. Biol. Chem.* 119: 473, 1937; *Jour. Biol. Chem.* 126: 595, 1938. (5) Hemingway, A., Pride, J., and Williams, R. T.: *Biochem. J.* 28: 136, 1934. (6) Marrian, G. F.: *Harvey Lectures*, 37. Williams and

during the excretory period. It must be stated that errors in collection, hydrolysis of the specimen, and errors in the technique of the determination must be kept in mind as possible explanations. Since only 2 of the 45 determinations done during the secretory stage showed no pregnanediol at the time when it should be present, these explanations seem adequate.

Table II shows graphically the relation between biopsy diagnosis and pregnanediol determination.

TABLE II. ENDOMETRIAL BIOPSY AND PREGNANEDIOL

BIOPSY DIAGNOSIS	NO.	PREGNANEDIOL PRESENT	PREGNANEDIOL ABSENT
Secretory	45	31	14 (12 within 2 days of menstruation)
Proliferative	15	0	15
Undiagnosed	5	3	2
Total	65	34	31

This series would indicate then that progesterone is excreted in the urine as sodium pregnanediol glucuronidate during the time that the endometrium is being activated to the secretory phase. It is, therefore, a valuable diagnostic adjunct in determining ovulation, especially since we feel that the endometrial biopsy may not always be accurate. Ten years ago Bartelmez²⁴ mentioned the fact that different parts of the uterine mucosa responded differently to either vascular or hormonal influences, and we have observed in biopsies taken with the small Meigs curette bits of endometrium from the same uterus which were considerably different in character. At least two biopsies have shown both proliferative and secretory characteristics from the same mucosa.

Whether different endometriums, or the same endometrium in different areas, may vary in their progestational responses is a question discussed by Wilson, Randall and Osterberg.¹⁶ Because of the great quantitative discrepancy in pregnanediol output in apparently normal women, they feel that some endometriums may need considerable progestational stimulation to undergo secretory changes, whereas others need only a small amount, in fact so little that the metabolic product, pregnanediol, may not even appear in the urine. They do not consider, however, the necessity for estrogenic proliferation of the endometrium, which must occur before secretory changes may take place, nor the fact that estrone acts concurrently with progesterone in the formation of a secretory endometrium.²⁵

There are so many variables in the process of progesterone metabolism and pregnanediol excretion that the amount of pregnanediol secretion cannot be considered any indication of the amount of progestational activity in the organism. It has been stated previously that the liver and kidney and other unknown factors all have a part to play in this transformation and excretion. Obviously, deficiency in any of these organs would result in decreased excretion without necessarily affecting the utilization and secretion of progesterone itself. In the second place, the mechanical factors involved, such as the collection of the urine and its preservation, and the technique of the process itself, make the quantitative result quite variable.

in 3 cases, from 102° to 103° in 4 cases, from 103° to 104° in 16 cases, and from 104° to 106° in 4 cases. Cases in the lowest temperature group were included because of other evidence of the severity of the infection. None of these patients had a positive blood culture. Five were intrapartum infections in three of which the temperature rose to 102° to 103° F. Two patients had peritonitis, and in two others pyelitis appeared to be associated with genital tract infection. A four-hour day and night schedule of 20 gr. of sulfanilamide was maintained through the night for two to six days in 24 cases, and eight, ten, and twelve days in 3 cases.

The clinical response to sulfanilamide therapy was good in 21 cases, doubtful in 5 cases and negative in 1. There were no deaths. In only one of the doubtful result cases had the streptococcus been identified. In 7 cases in which *Streptococcus hemolyticus* was demonstrated, results were good. In 6 out of 7 cases in which a streptococcus was positively identified as beta hemolyticus was found, and in 2 cases in which a nonhemolytic streptococcus was isolated, results were good. In 7 cases in which no streptococci were found, results were good in only 1. Streptococci were found in 16 cases and other organisms were rarely seen; *B. coli* in 2 cases, *B. proteus* in 1 case, and *Staphylococcus aureus* in 1 case. In 5 intrapartum infections response to sulfanilamide was doubtful in 1, and good in 4 cases in 2 of which *Streptococcus hemolyticus* was reported later.

COMMENT

These results are better than those we have previously reported and are additional evidence that sulfanilamide finds its greatest indication in *Streptococcus hemolyticus* infections. In severe infections sulfanilamide therapy need not wait upon bacteriologic investigation, yet this information is of some importance in deciding whether the drug should be continued in the absence of favorable clinical response. Sulfanilamide should not be used at all in mild cases of infection as it is unnecessary and probably useless. Douglas⁵ has found the hemolytic streptococcus in less than 1 per cent of puerperal infections, and insists that, with very few exceptions, accurate bacteriologic diagnosis before the commencement of therapy is all important. In severe infections, however, the problem is different, since the hemolytic streptococcus is the infective agent in a large number of these cases. Fry⁶ found that 33 per cent of all severe cases, and 70 per cent of all fatal cases were due to this organism. Group A does not include all the hemolytic streptococci pathogenic for man, for one of us (A. H. R.⁹) has reported two deaths in our service due to Groups B and C. Sulfanilamide failed in both cases, and in vitro and in vivo experiments indicated that it has no effect on these strains. So far as we know, all the strains of Group A respond to sulfanilamide therapy, but evidence in the case of infection by anaerobic streptococci, *Streptococcus viridans*, nonhemolytic streptococci, staphylococcus and *B. coli* is inconclusive. Time is an important factor in combating severe puerperal infection.

PYELITIS

We have given sulfanilamide to 17 patients with pyelitis, 12 ante-partum and 5 post-partum cases; 6 were primiparas and 11 multiparas. The dose of sulfanilamide in most cases was 20 gr. every four hours, but fluids were not definitely limited; titers ranged from 3.1 mg. to 8.5 mg.

Chills occurred in 8 cases, all ante-partum, though the highest temperatures were noted in the post-partum group, 2 reaching 104.4° F. In 10 cases temperature reached 103° F. In 2 cases there was no fever, but diagnosis was made on lumbar pain, kidney tenderness, and pyuria.

Wilkins, 1938-1939. (7) *Venning, E. H., and Browne, J. S. L.*: Endocrinology 21: 711, 1937. (8) *Hamblen, E. C., Ashley, C., and Baptist, M.*: Endocrinology 24: 1, 1939. (9) *Buxton, C. L., and Westphal, U.*: Proc. Soc. Exper. Biol. & Med. 41: 284, 1939. (10) *Westphal, U., and Buxton, C. L.*: Proc. Soc. Exper. Biol. & Med. 42: 749, 1939. (11) *Hartman, C. G., and Marker, R. E.*: Anat. Rec. J. Biol. Chem. 133: 529, 1940. (12) *Jones, H. W., and Weil, P. G.*: J. A. M. A. 111: 519, 1938. (13) *Venning, E. H., and Browne, J. S. L.*: J. Clin. Investigation 16: 678, 1937. (14) *Weil, P. G.*: Science 87: 72, 1938. (15) *Wilson, R. B., Randall, L. M., and Osterberg, A. E.*: AM. J. OBST. & GYN. 37: 59, 1939. (16) *Danforth, W. C.*: Illinois M. J. 7: 127, 1938. (17) *Elden, C. A.*: AM. J. OBST. & GYN. 35: 648, 1938. (18) *MacGregor, T. N., and Stewart, C. P.*: J. Obst. & Gynaec. Brit. Emp. 46: 857, 1939. (19) *Stover, R. F., and Pratt, J. P.*: Endocrinology 24: 29, 1939. (20) *Allen, E., Hisaw, F. L., and Gardner, W. U.*: Sex and Internal Secretions, ed. 2, 1939, p. 457. (21) *Engle, Earl T.*: Personal communication, 1939. (22) *Bartelmez, G. W.*: AM. J. OBST. & GYN. 21: 643, 1931. (23) *Engle, Earl T., and Smith, Philip E.*: Am. J. Anat. 63: 349, 1938.

THE USE OF SULFANILAMIDE IN OBSTETRICS AND GYNECOLOGY

A REPORT ON 121 CASES

CHARLES A. GORDON, M.D., F.A.C.S., AND
ALEXANDER H. ROSENTHAL, M.D., BROOKLYN, N. Y.

(From the Long Island College of Medicine Division, Kings County Hospital)

IN NOVEMBER, 1939⁷ we reported the results of sulfanilamide therapy in 118 patients with severe puerperal infections of the genital tract, 83 intrapartum or post-partum cases, and 35 cases of postabortal infection. Though careful bacteriologic investigation was carried out in most of these cases, treatment was not based on isolation of the *Streptococcus hemolyticus*. It had seemed probable from the work of Colebrook and his co-workers²⁻⁴ that little could be expected outside this group, yet clinical response in the entire series was convincing in 45 cases, or 38 per cent, and satisfactory though not so prompt in another 45 cases. We believe that in 76 per cent of these severe cases, sulfanilamide therapy was an important factor in the patient's recovery.

Since the prognosis of severe puerperal infection is grave, and the use of sulfanilamide involves no abandonment of any specific form of treatment, chemotherapy is indicated and need not depend entirely upon identification of the *Streptococcus hemolyticus*. In intrapartum infection, too, sulfanilamide has been given before report of the vaginal culture taken at the same time. Its hazards are definite but none of them need be serious if control is adequate. Though culture is routine in all post-partum patients whose temperature reaches 100.4° F., we have not treated minor febrile disturbances with sulfanilamide.

MATERIAL

Since our first report, 27 patients with severe puerperal infections have received sulfanilamide. It is so difficult to define the anatomic limits of these infections that cases have been classified clinically as severe by the same standard as heretofore; (1) high initial rise of temperature; (2) spiking temperature; (3) peritonitis; (4) chills; (5) spreading inflammation. Temperature ranged from 101° to 102° F.

We have evaluated our results by the clinical course of the patient, not from determination of bacilluria, though that should be helpful. The immediate response has been good, occasionally dramatic, for in 13 of our 17 cases subsidence of symptoms was rapid. Sulfanilamide would appear to be indicated, since it is excreted almost entirely by the kidneys, quickly diffusing into tissues flooded with urine. Concentration should occur with limited fluid intake. Our limited experience however indicates that it is but little better than other methods of treatment. We have not used chemotherapy in mild gynecologic infections of the urinary tract due to catheterization or contiguity as they seem to be self-limited.

MASTITIS

Mastitis, as a rule, is a mild infection yet it may be severe. The infective agent cannot be demonstrated unless suppuration occurs. If the breast fails to respond quickly to the ordinary treatment, sulfanilamide may be given with hope of success. We have given it to but 3 patients. It deserves consideration.

SEVERE PELVIC INFECTION (NONPUERPERAL)

For practical purposes pelvic inflammation is of puerperal origin or due to gonorrhea or instrumentation, though it may occur, of course, as a result of extension of infection outside the genital tract. A large number of acute infections become chronic. The characteristic lesion of pelvic gonorrhea is the pyosalpinx, with or without involvement of the ovary. Cellulitis is usually due to the streptococcus, staphylococcus or *B. coli*, and rarely to the gonococcus alone. Severe re-infections or exacerbations occur rarely in the typical cellulitic lesion, but are common in mixed infections. Studdiford, Caspar and Seadron¹⁰ have shown that gonococci may survive in the tubes for many years. It is likely that anaerobes play but a small part in the absence of necrotic tissue, and since Fry⁶ has shown that the normal genital tract is not a favorable situation for survival of *Streptococcus hemolyticus* Group A, the presence of these organisms depends upon instrumentation or previous puerperal invasion.

The management of 450 to 500 cases of pelvic infection admitted yearly to our gynecologic wards is our most formidable problem. Surgery as a rule is not indicated, and we have operated only for prolonged and increasing menorrhagia, severe dyspareunia of long standing, and serious disability. Partial operations are rarely curative, but treatment of external foci of infection is of great importance. We have learned to recognize ovarian abscess as a serious complication, and so drain it rather promptly. Cellulitis yields but little to conservative treatment. In fact our entire experience with treatment such as foreign proteins, diathermy, Elliott treatment, transfusions and the like has been very discouraging. Iontophoresis, however, seems promising. Since January, 1938, we have given sulfanilamide therapy a trial, hoping for good results, yet expecting little in the resolution of hard fibrotic or cellulitic lesions, since diffusion of the drug into these tissues should be difficult. As yet we have not used it in chancroid infection or lymphogranuloma.

Early in our work sulfanilamide was given in doses of 80 gr. a day for two days, 60 gr. daily for the next three days, and 40 gr. daily thereafter (39 cases), or 120 gr. a day for two days, 80 gr. daily for the next three days, and 60 gr. a day thereafter (24 cases). Later it was administered in 20 gr. doses every four hours day and night with restriction of fluids. Blood titers have been fairly consistent.

In reporting 74 cases we have included 13 from the service of Dr. Alfred C. Beck at the Long Island College Hospital*; 27 patients were white and 47 negro. All infections were severe enough for hospitalization. As clinical evidence of severity, 46 patients had single or bilateral pelvic masses; fever of 101° to 105° F. was present in 60 cases, with temperature of 103° to 105° F. in 31 cases; general peritonitis was present in 1 case, and marked pelvic peritonitis in 21. In 23 cases external lesions of gonococcal infections as urethritis, Skenitis, and Bartholinitis were seen, and in 4 cases acute cervicitis. Smears for the gonococcus were positive in

*We are indebted to Drs. Harvey B. Matthews, William A. Jewett, and George W. Phelan for these cases.

Toxemia was present in 3 cases. In 2 of these the patient was admitted for toxemia and developed pyelitis on the ward. In the third case, although the patient was admitted for pyelitis, she had been admitted for toxemia earlier in the same pregnancy. In the other 11 cases there was no evidence of toxemia or diminished renal function; urea clearance, Fishberg and blood chemistry tests were repeatedly done.

In the 17 cases, blood culture was positive for a gram-negative bacillus in 1, and the urine was cultured in 13 cases and found positive in 11. *B. coli* was found in 8 cases, associated with a nonhemolytic streptococcus in 2, with *B. proteus* 1, and *Staphylococcus aureus* 1; other organisms were nonhemolytic streptococcus 1, *B. proteus* 1, pneumococcus 1.

Respiratory infection was present in 4 cases, pharyngitis 2, bronchitis 1, and bronchopneumonia 1. In this case the pneumococcus was cultured from the urine. This patient, admitted in the eighth month of pregnancy for bronchopneumonia and pyelitis, responded well in two days to 160 gr. of sulfanilamide. She was readmitted the day after discharge with pyelitis more severe than the first infection, temperature reaching 105.6° F. with repeated chills. She again responded to sulfanilamide therapy. In the other 3 respiratory infections with pyelitis, *B. coli* was cultured in the urine of 2 cases, and a nonhemolytic streptococcus in 1.

The 5 post-partum cases did well with sulfanilamide. Detailed clinical data in 12 ante-partum cases are tabulated in Table I.

TABLE I. SULFANILAMIDE THERAPY—ANTE-PARTUM PYELITIS

	PERIOD OF GESTATION MONTHS	SULFANILAMIDE			RECURRENCE OF PYELITIS
		GRAINS GIVEN	DAYS GIVEN	RESULTS	
1	5	240	3	Good	Not yet delivered
2	Term	480	5	Good	
3		755	9		
	7	390	6	None	Two recurrences in seventh month
	7	580	7		
4	8	400	4	Good	Not yet delivered
5	6	460	6	Good	
6	7	360	3	None	Two recurrences post partum
7	5	240	4	None	Two recurrences, seventh month and post partum
	7	380	4		
8	8	160	2	None	Recurred post partum
9	6	200	2	Good	Pyelitis 2 yr. previous
10	8	120	2	Good	Previous pyelitis
11	Term	540	6	Good	
12	5	240	2	Good	Not yet delivered

Infection of the urinary tract is a common complication of pregnancy. Pyelonephritis is serious and may cause death. Coliform bacilli are the usual infective agents, yet here as elsewhere other organisms may cause severe infections, and should be thought of when pyelitis is associated with upper respiratory infection. The objectives of treatment are urinary antisepsis and relief of stasis. Intravenous pyelography and cystoscopy should be reserved for intractable cases. Fortunately most infections improve on any type of treatment, even bed rest alone. Subsidence of symptoms does not mean cure, nor is a sterile urine culture a satisfactory criterion. Long follow-up, perhaps only through another pregnancy, is necessary. In our small group of 12 ante-partum cases, with 3 as yet undelivered, pyelitis has recurred during the same pregnancy or in the puerperium in 4. In all probability recurrence may be expected in this group.

One patient in this group with severe pyelitis in the third month responded well to 755 gr. of sulfanilamide over a nine-day period. On readmission in the seventh month with another severe attack, she was given 390 gr. in six days and her symptoms disappeared, but recurred three days later; she was then given 580 gr. during the next seven days. Shortly afterward she was delivered prematurely, showing no recurrence in the puerperium.

(3) M. V., aged 25 years, negress, had a vulvovaginitis and salpingo-oophoritis. She was given 525 gr. of sulfanilamide in seven days without much improvement. Smears remained positive, though blood titers reached 11.8 mg. and 11.3 mg.

(4) D. W., aged 19 years, was admitted with gonococcal urethritis, cervicitis, and pelvic pain but no fever. She received 585 gr. of sulfanilamide in eight days. On the seventh day however, temperature rose to 104° F., with evidence of severe pelvic peritonitis. Since sulfanilamide had failed to stop progress of her infection under optimal conditions, it was discontinued. She improved slowly, smears remaining positive three weeks after admission.

TABLE II. RESULTS OF THERAPY

	TOTAL NO. OF CASES	SATISFAC- TORY	DOUBTFUL	UNSATIS- FACTORY
Cellulitic infection	12	1	3	8
Abdominopelvic abscess	6	1	1	4
Primary gonococcal infection	11	6	2	3
Acute exacerbation of chronic disease	30	5	16	9
Difficult to classify	15	4	9	2
	74	17 -23%	31	26

It is impossible to set up proper control series for these types of infection. Evaluation of therapy is based on the course of the patient in the hospital. It is common experience to see patients improve on bed rest alone, even with resolution of inflammatory masses. We could easily show such a series. Unusually rapid subsidence of fever, disappearance of abdominal tenderness and rigidity, relief from pain and diminution in size of pelvic masses were our criteria of satisfactory response to chemotherapy. When the clinical course of the disease coincided with previous experience, it was difficult to assess the value of therapy, so we have called this result doubtful. When the patient did not improve or became worse, obviously sulfanilamide was without value.

Reports of gynecologic infections other than primary gonococcal infections are scant and limited to but few cases. Grodberg and Carey⁸ have reported resolution of tuboovarian masses in ten to fourteen days. Bomze, Fuerstner and Falls,¹ in 45 cases treated in the out-patient clinic, observed resolution of large inflammatory masses in 3 cases after four to six weeks. In Douglas's gonorrhea cases, only 1 had inflammatory pelvic disease with masses.

Our failure with chemotherapy in pelvic inflammation of long standing is not surprising. Success depends upon the nature of the organism, proper concentration of the drug in the blood and easy diffusion into the diseased tissues. We are also impressed with the failure of chemotherapy, in our experience, in puerperal infection with vegetative endocarditis, or when placental fragments or polyps are present in the uterus. Thus the character of the lesion is of great importance. We have observed no notable diminution in the size of pelvic masses. A satisfactory result in 74 cases occurred in but 17, and in 11 of these, success was probably due to the presence of the gonococcus. However only 6 out of 11 primary gonococcal infections responded satisfactorily. No doubt this is the best form of therapy we have and failure or sharp re-invasion while under treatment is probably due to the presence of nonspecific organisms. Cultures as evidence of cure are no doubt superior to smears, as Douglas⁵ points out. Complement fixation has a practical value in that persistence of a strongly positive reaction indicates a latent focus, even though cultures are negative. Cellulitis and the common fibrotic and cystic changes occurring in tuboovarian masses cannot reasonably be expected to respond to sulfanilamide therapy. The most enthusiastic advocates of chemotherapy in the male admit its failure in nonspecific prostatitis and epididymitis. These lesions correspond to the common form of inflammatory tuboovarian masses in the female, for in the genital adnexa of both sexes, nonspecific organisms follow the invasion of the gonococcus, and accumulations of pus surrounded by fibrotic tissue will not permit diffusion of the drug.

13 cases, and complement fixation was positive in 26. In 15 cases apparently of gonorrheal origin complement fixation was negative, yet smears were positive in 3.

DIAGNOSIS

Acute exacerbation of chronic pelvic inflammation	30
Salpingo-oophoritis (includes the above)	56
With pelvic peritonitis	21
With general peritonitis	1
Cellulitis	4
With salpingo-oophoritis	5
With salpingo-oophoritis and pelvic abscess	2
With peritonitis	1
Abdominopelvic abscess	3
Abdominopelvic abscesses (multiple)	3

The age of these patients is of interest, as in our experience incidence of chronic pelvic inflammatory disease diminishes as women grow older, and its lesions usually become symptomless or cured with menopause; 56 were less than 35 years of age, 7 between 35 and 40, 9 between 40 and 45, and 2 between 45 and 50. None had passed the menopause; pelvic masses or fever rarely occur in postmenopausal gonorrhea. The age of the infection may, as a rule, be determined with fair accuracy from the history.

AGE OF THE INFECTION

Less than 3 months	22
3 months to 1 year	6
1 year to 4 years	12
4 years or longer	12
Old infection (age unknown)	8
Not determined	14

On the whole, results were disappointing. Chemotherapy was unsatisfactory in cellulitic infections and abdominopelvic abscess, somewhat successful in acute exacerbations of chronic pelvic inflammation, and satisfactory only in cases of primary gonococcal infection. But even in primary gonorrhea it was impossible to predict good results with any certainty. A brief discussion of a few typical cases will illustrate.

A. Cellulitic Infection.—H. K., aged 18 years, had a huge cellulitic mass, and the etiology was obscure. She received 725 gr. of sulfanilamide with no effect on her severe septic course or on the size of the exudate.

B. Abdominopelvic Abscess.—(1) I. F., aged 31 years, negress, had been operated upon for salpingitis five years previously. She presented on admission a large tuboovarian abscess with septic temperature often reaching 104° F.; sulfanilamide failed and she improved only after colpotomy.

(2) J. A., aged 32 years, who had been operated upon for ovarian abscess seven years before admission, was admitted with abdominopelvic abscess and septic temperature. She became worse under therapy but recovered after abdominal drainage of two abscesses at two independent operations.

(3) E. C., aged 41 years, had a pelvic infection with gonococcal smear positive; 600 gr. of sulfanilamide were given in 7 days. She became worse, developing a pelvic abscess which was drained vaginally; pus showed a pure culture of *Staphylococcus aureus*. Death occurred one day later.

C. Primary Gonococcal Infection.—(1) O. G., aged 24 years, negress, had acute salpingitis with positive gonococcal smear; 530 gr. of sulfanilamide were given in seven days with striking improvement. Temperature which had been 102° F. for two days became normal the day after chemotherapy was begun and remained so.

(2) E. B., aged 25 years, negress, was admitted with a temperature of 104° F., Skenitis, Bartholinitis, and small tender adnexal masses. She responded well to 765 gr. of sulfanilamide, temperature becoming normal and smears negative.

pelvic infections with tuboovarian masses when the gonococcus cannot be demonstrated. Evidence accumulates that sulfanilamide should not be given to ambulatory patients.

REFERENCES

- (1) *Bomze, E. J., Fuerstner, P. G., and Falls, F. H.*: AM. J. OBST. & GYNEC. 38: 73, 1939. (2) *Colebrook, L., and Hare, R.*: Brit. M. J. 2: 723, 1930. (3) *Colebrook, L., and Maxted, W. R.*: J. Obst. & Gynaec. Brit. Emp. 40: 966, 1933. (4) *Colebrook, L., and Purdie, A. W.*: Lancet 2: 1237 and 1291, 1937. (5) *Douglas, R. G.*: AM. J. OBST. & GYNEC. 39: 275, 1940. (6) *Fry, R. M.*: Brit. M. J. 2: 340, 1938. (7) *Gordon, C. A., and Rosenthal, A. H.*: Surg. Gynec. Obst. 69: 631, 1939. (8) *Grodberg, B. C., and Carey, E. L.*: New England M. J. 218: 1092, 1938. (9) *Rosenthal, A. H.*: J. A. M. A. 114: 840, 1940. (10) *Studdiford, W. E., Caspar, W. A., and Scadron, E. N.*: Surg. Gynec. Obst. 67: 176, 1938.

256 JEFFERSON AVENUE
61 EASTERN PARKWAY

THE SIGNIFICANCE OF THE TUBERCULIN TEST IN PREGNANCY*

EDWARD C. MAEDER, M.D., PH.D., AND J. ARTHUR MYERS, M.D., PH.D.,
MINNEAPOLIS, MINN.

(From the Minneapolis General Hospital, the Departments of Obstetrics and Gynecology, Preventive Medicine and Internal Medicine, University of Minnesota, and the Lymanhurst Health Center)

IN THE midwestern part of this country, where our work was done, only about 25 per cent of the girls of college age have been infected with tubercle bacilli. At present the infection attack rate even in the cities is only approximately 1 per cent each year. Therefore, the girls attain the usual age of motherhood with 75 per cent or more free from tuberculous infection. To us the term "tuberculous infection" always means the presence of at least one primary tuberculosis complex, which consists of the primary lesion and those in the regional lymph nodes. Such lesions are usually small and rarely have they, per se, resulted in significant clinical tuberculosis.

On the basis of longitudinal studies of infected persons and on the basis of morbidity and mortality, it now appears that at least 25 per cent and probably more persons infected with tubercle bacilli have clinical manifestations of the disease at some subsequent time. In one group of children who reacted to tuberculin at the average age of eight years, it was found that by the time they had attained the average age of twenty-five years, 15 per cent had developed clinical tuberculosis.¹ (From 5 to 10 per cent of the deaths in this country are due to tuberculosis.) On the basis of results of extensive tuberculin testing of healthy appearing persons, it has been estimated that not more and probably less

*Prepared with the aid of a grant from the medical research fund, University of Minnesota.

We are deeply indebted to Miss Elizabeth Sprague, R.N., Director of Tuberculosis Control, Minneapolis Health Department, and her staff for the large volume of follow-up work done and the assembling of data.

TOXIC MANIFESTATIONS

There were no deaths due to sulfanilamide therapy. Toxic symptoms were noted as in our previous series of 118 cases in about half of the cases. One case of acute hemolytic anemia occurred in a sixteen-year-old negress with primary gonococcal infection, after administration of 330 gr. of sulfanilamide, 120 gr. on the first and second days, and 90 gr. on the third, when the hemoglobin dropped from 65 per cent Sahli to 55 per cent; chemotherapy was discontinued, but three days later hemoglobin was 24 per cent; she responded well to transfusions. The appearance of jaundice and increased amounts of urobilin may exceptionally be preceded by actual hemoglobinuria. We have not seen agranulocytosis as it apparently occurs only after longer treatment than we have thought wise. We have observed jaundice in three cases without confirmatory evidence of hemolytic anemia; in one of these patients with considerable tenderness over the liver, it was thought to be due to toxic hepatitis, the icterus index reaching 143 units.

Our complete clinical results in obstetrics and gynecology are shown in Table III.

TABLE III. CLINICAL RESULTS OF CHEMOTHERAPY IN OBSTETRICS AND GYNECOLOGY
121 SEVERE INFECTIONS

INFECTIONS	TOTAL NO. OF CASES	RESPONSE TO SULFANILAMIDE		
		GOOD	DOUBTFUL	NONE
<i>Puerperal:</i>				
Post partum	22	17	4	1
Intra partum	5	4	1	—
Pyelitis	17	13	—	4
Mastitis	3	—	—	—
<i>Gynecologic:</i>				
Cellulitis	12	1	3	8
Abdominopelvic abscess	6	1	1	4
Primary gonococcal infection	11	6	2	3
Exacerbation of chronic pelvic infection	30	5	16	9
Unclassified pelvic infection	15	4	9	2
Total	121			

CONCLUSIONS

In minor febrile disturbances chemotherapy should not be used. In severe intrapartum and puerperal infections of the genital tract, sulfanilamide should be given provided the patient is in a hospital where its administration may be properly controlled. Bacteriologic diagnosis need not precede therapy, yet early recognition of the infective agent is important. Since it is probable that sulfanilamide is effective only when the *Streptococcus hemolyticus* Group A is present, administration should not be continued for longer than a week, if another organism has been isolated.

In mastitis not responding to ordinary treatment, chemotherapy should be tried. In pyelitis it is at least as effective as other methods of drug treatment. A large series of cases followed over a considerable period of time will be necessary before positive statements can be made.

Sulfanilamide should be used in gynecologic infections (1) if they are primary gonococcal, (2) if smear or culture is positive with exacerbation or reinfection of old gonococcal infection, and (3) when the *Streptococcus hemolyticus* can be demonstrated as the infective agent.

Sulfanilamide should not be given in cases of cellulitis, pelvic or abdominopelvic abscess or to patients with acute exacerbations of chronic

cause of adhesions, strict bed rest, preferably in a hospital or a sanatorium, should be strongly recommended.

A tuberculous mother should be kept under close observation following delivery whether her disease is manifested only by a tuberculin reaction or whether definite clinical lesions can be located. If a tuberculin reaction only is present, x-ray films should be made every three to six months for a year, following which no year should be allowed to pass without a complete examination. If clinical lesions be present before delivery, active treatment should be continued as long as may be necessary. Those whose disease cannot be rendered non-contagious should be kept under strict isolation in a hospital or a sanatorium.

An equally important problem is the welfare of the infant. The source of tuberculous pneumonia, meningitis, and miliary disease in infants and small children who died is usually found to be contagious tuberculosis in the home or among relatives in close contact with the child. Often the infected contact had the disease in unsuspected form or was unaware of the danger of contagion.

Almost all tuberculous infants acquire the disease as a postnatal infection. The immediate removal of the newborn from the mother with contagious tuberculosis cannot be too strongly emphasized. If this is not done one must expect a high incidence of infection.

Most infants and children have but a few close adult contacts. It is usually only adults who have pulmonary tuberculosis in the contagious stage. The problem of preventing tuberculous infection is relatively simple and is a matter of recognizing and controlling the possible sources of infection.

The solution of the problem of tuberculosis in mother and infant begins with the examination of the pregnant woman for tuberculosis. These women readily submit to such examination because they are solicitous for the health of their offspring and themselves. This will reveal practically all primary tuberculosis complexes. Even though no clinical disease be present these are potential cases of clinical tuberculosis and they should know it. Those who have clinical lesions in the pre-symptom stage will be found and may be treated. Moreover, some would be found who already have the disease in the contagious stage. If they have advanced lesions, their infants may be protected against infection following delivery.

In April, 1934, a desperately ill infant of six months was admitted to the Minneapolis General Hospital. This infant had acute fatal tuberculosis. In seeking the source, the mother was found to have extensive tuberculosis, involving the left lung. Tubercle bacilli were abundantly present in her sputum. She had been in the General Hospital for delivery but no examination had been made for tuberculosis. This infant's infection should have been prevented. The treatment of the mother should have been instituted many months earlier than it was, although she was sent to a sanatorium as soon as she was recognized to be the source of her child's infection. She is still there and her condition appears hopeless. This case was brought to the attention of the late Dr. John Urner, who was chief of the Obstetrical Service of the

than 50 per cent of the population, including all ages, are infected with tubercle bacilli. Thus, 10 to 20 per cent of the infected die from this disease, and it becomes obvious that tuberculous infection is a serious matter.

The examination of the woman who presents herself for obstetric care should include the tuberculin test, just as certainly as it should include a test for syphilis. Since reactors to tuberculin have lesions of primary complexes, the physician should immediately examine such persons with the greatest of care for the presence of clinical tuberculosis.¹² If this disease happens to be in the lungs or kidneys, it usually is easily detected by x-ray, clinical and laboratory examination; if it be in the pelvic organs it may be more difficult of recognition unless it involves large areas. A single search for clinical tuberculosis in the pregnant woman does not suffice. Those who react to tuberculin may be entirely free from this form of the disease today, but it may make its appearance at any subsequent time.

The effect of pregnancy on tuberculosis has been extensively discussed in the literature.¹⁰ Many views have been expressed by such workers as Dumarest,² Flick,⁴ Jameson,⁸ Jennings, Mariette, and Litzenberg,⁹ and Rist.¹⁴

Much that has been said about tuberculosis and pregnancy has been based upon personal opinion rather than scientific observations. Thus, there is no incontrovertible evidence that pregnancy has any effect on tuberculous lesions of the primary complex, but it has been suggested that it does in some cases. Therefore, the pregnant women who react to tuberculin should be examined with extreme care.

The woman with a tuberculous focus, no matter how small and regardless of type, is not as good a risk as the woman who is entirely free from tuberculosis. This applies to any person regardless of pregnancy. Therefore, the physician can never determine with accuracy just when it is safe for a woman with a tuberculous lesion to become pregnant. It must always be a matter of opinion and judgment and each case must be decided upon its merits.

The treatment of pulmonary tuberculosis has advanced rapidly in the last few years and special methods have been devised for bringing the disease under control so that many women in whom termination of pregnancy might have been indicated in the past are now able to go through one or more pregnancies with no apparent effect on their tuberculosis. Collapse therapy has more value in tuberculosis therapeutics than all the other measures combined, and this is particularly true for the pregnant tuberculous woman. If progressive minimal or early, moderately advanced clinical tuberculosis is found after pregnancy occurs, immediate treatment, such as artificial pneumothorax, should be instituted. When the diseased area in the lung is collapsed, many women are able to continue with pregnancy with no deleterious results. Thus, from the standpoint of the health of the pregnant woman herself, it is of extreme importance that an adequate examination be made for tuberculosis. If the patient's disease is too advanced or the lung cannot be collapsed be-

TABLE II. REINFECTION TYPE OF TUBERCULOSIS

Minimal	17
Moderately advanced	4
Far advanced	5
Total	26
Disease present on first examination	21
Disease appeared during pregnancy	2
Disease appeared subsequent to pregnancy	3
Extrapulmonary tuberculosis	
Renal with nephrectomy	1
Laryngitis	1
Enteritis	2
Peritonitis	1
Miliary	1
Treatment	
Sanatorium	9
Collapse therapy	4
Well-regulated life under close observation	13
Deaths	2

As helpful as the x-ray examination is in locating areas of disease, the findings on a single inspection can never constitute a diagnosis. For example, 2 of the women who reacted to tuberculin had shadows which were reported as tuberculosis, and cavity formation was mentioned. In each case the shadows completely disappeared within a month. These women had pneumonia which had not completely resolved when we first saw them, but the areas in which resolution was occurring were interpreted as cavities; therefore, whenever shadows were observed on the first x-ray film, we refrained from making definite diagnoses until adequate evidence was available.

A careful search, including cultures and animal inoculations, was made for tubercle bacilli in sputum when available. When this study began, we did not examine gastric washings of patients in whom bacilli could not be found by direct examination. However, we now strongly recommend this laboratory method. Serial x-ray films were made. When shadows persisted more than four to six weeks, we considered them due to tuberculosis, in spite of the possibility of error, since not all persistent shadows in adults are caused by this disease.

Some workers have used the fluoroscope as the first screen and x-ray films are made only of the chests of those persons who have definite or questionable shadows revealed on the screen. For example, Eisele and Mason³ examined 4,040 apparently normal pregnant women in this manner and found 43 cases of previously unsuspected tuberculosis in 28 of whom the disease was progressive.

Ianne⁶ used the tuberculin test and x-ray films of the reactors in the examination of 691 pregnant women, of whom 284 (41 plus per cent) reacted to tuberculin. Two hundred and fifty-two of the reactors were x-rayed. The x-ray revealed 12 cases of the reinfection type of disease. Of these, 10 were in the minimal, 1 in the moderately advanced, and 1 in the far-advanced stage of tuberculosis.

Hilleboe⁵ has called attention to the work of G. Kjellin of Stockholm, Sweden, who has examined 100,00 pregnant women for tuberculosis and found 13 per cent with clinical tuberculosis. Thus, from available evidence it appears that slightly more than 1 per cent of pregnant women, who have been examined, have clinical tuberculosis requiring close observation or treatment.

COMMENTS

In 1937, there were born in the United States 2,203,337 infants. If 1 per cent of the mothers had clinical tuberculosis, more than 20,000 cases could have been discovered that year. It is doubtful whether more than a very small percentage of this number was actually dis-

Minneapolis General Hospital. He immediately visualized the problem and made an arrangement whereby all the women who presented themselves for obstetric care in his out-patient department would be referred to our chest clinic. In 1934 the obstetric and tuberculosis divisions of the Minneapolis General Hospital organized a special clinic to assure careful study of patients presenting themselves for prenatal care. The following is a report of the procedure and experiences of the clinic since that time.

CLINICAL PROCEDURES

The procedure in the clinic consisted of administering 0.1 mg. of tuberculin intracutaneously to all patients. The usual second dose of 1.0 mg. was not used because of difficulty encountered in getting the patients to return at short intervals. It is strongly recommended when possible that the second dose be administered when there is no reaction to the first dose within seventy-two hours. Those who reacted to tuberculin were sent to the x-ray laboratory for a film of the chest. Reports of the findings were prepared by the roentgenologists, after which both the reports and the films were sent to our clinic. At the time the patient returned, regardless of the findings on the film, an opportunity presented itself to impress upon the expectant mothers the importance of creating conditions in the homes which would prevent their infants from developing contagious diseases, especially tuberculosis.

From June 1, 1934, to July 1, 1938, a total of 2,350 pregnant women were examined in our clinic. Of those, 1,491 did not react to tuberculin and 18 did not have the tests read (Table I). It is reasonably safe to conclude that the negative reactors had no tuberculosis problem at the moment. X-ray films were made of the chests of the 841 who reacted to tuberculin, but no evidence of disease was seen in 679 (Table I).

TABLE I. NUMBER RECEIVING TUBERCULIN TEST AND HAVING X-RAY FILM INSPECTION

Tuberculin reactors	841
Tuberculin non-reactors	1491
Tests not read	18
X-ray film examinations	841
No abnormal x-ray findings	679
Possible primary complex revealed by x-ray	135
Probable reinfection type lesions	26

These persons were informed that they had at least one primary tuberculosis complex, and although the lungs were clear to x-ray examination at that moment there was no guarantee that they would remain clear. It was explained that the examination was limited to the lungs because this is the most common site of the reinfection chronic form of tuberculosis. When the disease develops in the lungs it is likely to become contagious. They should therefore keep under observation not only through the present pregnancy but throughout life. Of the 841 tuberculin reactors, 135 had shadows on the x-ray film interpreted as representing deposits of calcium. The majority represented primary tuberculosis complexes. Those with such findings were given the same instructions as the tuberculin reactors who had clear chest films, since we recognized that this is a group who had had primary complexes of such size and so located that they could be visualized by this method, while the others had smaller or similar processes which were not visualized or were in other locations. Of the 841 tuberculin reactors, 26 (3.1 per cent) had shadows on the x-ray film which were thought to be due to chronic tuberculous lesions. Of these, 17 were classified as minimal, 4 as moderately advanced, and 5 as far advanced (Table II).

tubercle bacilli were found in her sputum and guinea pig inoculation from a specimen of stool was negative. Nevertheless, she had a diagnosis of tuberculous enteritis. In June, 1938, she left the institution against the advice of the medical staff. Although her condition was definitely improved by treatment, the staff considered her prognosis unfavorable. She was readmitted to the Minneapolis General Hospital on June 20, 1938, with intestinal hemorrhage and died the same day. Here we have a case of extensive pulmonary tuberculosis which was only first suspected and discovered through the use of the tuberculin test during pregnancy.

CASE 3.—E. R., 23 years old, gravida iv, para iii, was admitted to the hospital in November, 1937. Her pregnancy was at term, and she delivered normally with episiotomy and repair. The puerperium was uneventful and she left the hospital on the ninth day. In November, 1937, she reacted to tuberculin, but a physical and fluoroscopic examination of her chest revealed no evidence of disease. However, in April, 1938, an x-ray film examination revealed evidence of minimal disease in the left lung. No tubercle bacilli could be found in her sputum. In December, 1938, she was admitted to a sanatorium with far-advanced pulmonary tuberculosis, with cavitation in the left lung. She also had tuberculous laryngitis. At this time tubercle bacilli were found in her sputum. Artificial pneumothorax was attempted but adhesions prevented a satisfactory collapse. Intrapleural pneumolysis was done in February, 1939. She is still in the sanatorium and her prognosis is now thought to be favorable. This case illustrates the fact that the tuberculin test is superior to the physical and fluoroscopic examination in determining the presence of tuberculosis. It is possible that an x-ray film of her chest might have revealed evidence of disease in November, 1937. Again, the lesion may have been so small at that time that it escaped detection. Nevertheless, the film should have been made, as it is far superior to physical examination and to the usual fluoroscopic examination.

CASE 4.—D. H. In March, 1936, this woman of 29 years reacted to the tuberculin test. The x-ray film examination of her chest revealed evidence of a small lesion in the left upper lung field. She was admitted to a sanatorium in May, 1936, where the x-ray film revealed no change in the shadow seen in March. In July, 1936, as gravida iii, para ii, she delivered a full-term infant at the sanatorium. During her stay in the sanatorium, tubercle bacilli were not found in her sputum. However, tuberculosis of the left kidney was diagnosed and tubercle bacilli were recovered from a specimen of urine from the left ureter. She left the sanatorium against the advice of the medical staff in August, 1937, at which time the disease in the left upper lobe had decreased considerably. On October, 1937, she was readmitted to the sanatorium and nephrectomy was performed. Miliary tuberculosis was found in the left renal pelvis and ureter. No tubercle bacilli have been found in her sputum. The pulmonary lesion remained unchanged. She was discharged from the sanatorium with four hours exercise in November, 1938. This case demonstrates the fact that tuberculous lesions may be multiple and, therefore, the examination of the chest alone does not always suffice. Clinical lesions may be present in other parts of the body. Here the pulmonary lesion was apparently stationary while the renal lesion was progressive.

CONCLUSIONS

1. The woman who enters upon the period of pregnancy with a tuberculin reaction is not as good a risk as the woman who is a non-reactor, since the tuberculin reaction indicates the presence of living tubercle bacilli in the body.

2. Routine tuberculin tests followed by x-ray films of the chests and complete examinations of the reactors as indicated should rank with routine Wassermann tests and complete examinations of the reactors as a medical necessity in pregnant women.

covered, inasmuch as without modern methods of examination, including the tuberculin test and the x-ray film, only the more advanced cases with symptoms and abnormal physical signs come to light.

Thus, careful examinations of all pregnant women not only insure the finding of minimal tuberculous lesions, when treatment of the mother is of most avail, but also should prevent large numbers of infants from becoming infected and thus avoid the immediate and remote hazards.¹² This examination should extend to the adult members of the entire household, as well as nurses, physicians, and in fact, everyone who comes in contact with the infant. When this is done, the infant will be born in an environment free from contagious tuberculosis and meningitis, miliary tuberculosis, and tuberculous pneumonia, so fatal to infants, will become rarities.

Conservation was the keynote in the obstetric management of our patients. The conduct of labor was closely supervised with the purpose of conserving the mother's energy. Maternal exhaustion during labor was avoided. Great care was exercised toward making labor as short, quiet, and effortless as possible. This was accomplished by giving proper rest through the judicious and conservative use of analgesics and anesthesia and by seeing that the patient received proper nourishment during labor. Local anesthesia is preferred for surgical obstetric procedures. Prophylactic forceps delivery as soon as the cervix is completely dilated conserves the patient's energy by avoiding the expulsive effort during the second stage of labor. No cesarean sections were performed in our group.

CASE REPORTS

CASE 1.—L. B. In November, 1936, this woman of 22 years reacted to tuberculin, but the x-ray film of her chest revealed no evidence of disease. In February, 1937, she was admitted to the hospital as gravida i. The delivery was normal and the puerperium uneventful. In April, 1938, she was readmitted to the hospital and found to have bilateral pleurisy with effusion. Tuberculosis was strongly suspected, but smears made from the pleural fluid revealed no tubercle bacilli, and guinea pig inoculation was negative. At this time no evidence of disease could be seen in either lung on the x-ray film. Re-examination in July, 1938, revealed evidence of thickened pleura but the lung parenchyma was apparently clear. On Sept. 14, 1938, she was acutely ill and was readmitted to the hospital. At this time, the x-ray film examination of her chest revealed shadows suggestive of miliary tuberculosis. Guinea pig inoculation of sputum was later reported positive for tuberculosis. She delivered an eight-month, premature, living infant on Sept. 17, 1938, after labor of two and one-half hours. She had had no prenatal care. She died in September, 1938, and the post-mortem examination revealed miliary tuberculosis, tuberculous pneumonia, and tuberculous enteritis. This is a good example of a woman who had tuberculosis in November, 1936, as manifested by the tuberculin test but other phases of the examination, including the x-ray film of her chest, were not sufficiently delicate to determine its location.

CASE 2.—E. P. This woman, 32 years old, gravida i, was found to react to the tuberculin test in April, 1937. She was admitted to the Minneapolis General Hospital May 8, 1937, and delivered normally with episiotomy and repair. Following delivery her daily temperature varied from normal to 100° F. The x-ray film examination of her chest in May, 1937, revealed evidence of extensive disease in both lungs which proved to be due to tuberculosis. On May 19, 1937, she was discharged to a sanatorium. An attempt was made to institute artificial pneumothorax on the left side, but adhesions prevented a successful collapse. No

Group II. Cephalopelvic disproportion and abnormal presentations were again recognized as contraindications to artificial rupture. Breech and transverse presentations were excluded from the analysis, since by selection they would all fall in Group I and might affect the results.

Group I included 308 primigravidas and 692 multigravidas; while in Group II the corresponding figures were 281 primigravidas and 719 multigravidas. There were 47 patients with minor degrees of pelvic contraction (simple flat, 10; generally contracted, 11; and funnel, 26), in none of whom was there any evidence of disproportion. The recorded presentations as shown in Table I indicate an unusual percentage of occiput anteriors, but the distribution between right and left occiput positions seems reasonably accurate.

Analgesia and Anesthesia.—Some form of sedation was given during labor to 307 individuals in Group I (morphine and scopolamine, 176; morphine, 26; various barbituric acid derivatives, 74; pentobarbital and scopolamine, 24; and rectal ether, 7); and to 364 patients in Group II (morphine and scopolamine, 255; morphine, 27; various barbituric acid derivatives, 55; pentobarbital and scopolamine, 16; rectal ether, 11). In the remaining 1,329 cases, mostly multigravidas, no sedative drugs were administered.

TABLE I. ANALYSIS OF CEPHALIC POSITIONS IN THE TWO GROUPS

	NO DATA	L.O.A.	L.O.T.	L.O.P.	R.O.A.	R.O.T.	R.O.P.	BROW	FACE
Group I (Spontaneous)	8	499	34	21	354	36	43	2	3
Group II (Elective)	3	494	77	23	315	48	38	1	1

Some form of anesthesia was given to 1,881 individuals during the second stage, usually as the head was coming over the perineum; in the remaining 115 patients, delivery was too rapid to permit anesthetization. In four instances there were no data. Ethylene was used alone in 1,716 cases, and with ether in 47; nitrous oxide was given to 19 patients, open ether to 31, chloroform to 34, cyclopropane to 2, and local infiltration was employed 32 times. The distribution was approximately the same in the two groups and is probably without any real significance in relation to the factors studied.

TABLE II. COMPLICATIONS OF LABOR

	GROUP I (SPONTANEOUS)	GROUP II (ELECTIVE)
Complications absent	930	930
Complications present	70	70
Intrapartum infection	13	25
Post-partum hemorrhage	46	34
Retained placenta	3	2
Prolapse of cord	2	4
Maternal exhaustion	5	1
Prolapse of arm	1	4

Complications of Labor.—Table II enumerates the various complications of labor, other than the prolongation of parturition beyond thirty hours, in the two groups. It will be noted especially that intrapartum infection was approximately twice as frequent in Group II as in Group I, presumably because long latent periods predispose to uterine infection before delivery. On the other hand, there were 50 per cent more post-partum hemorrhages in Group I than in Group II, a fact for which

3. The pregnant woman with tuberculosis should receive whatever treatment is indicated throughout the period of pregnancy and for as long thereafter as necessary. Collapse therapy is valuable when indicated.

4. The offspring of mothers with tuberculosis should have no contact with the mother as long as her disease is contagious.

5. Tuberculous foci may appear or extend during or following pregnancy.

REFERENCES

- (1) *Ch'iu, T. Y., Myers, J. A., and Stewart, C. A.*: J. A. M. A. 112: 1306, 1939. (2) *Dumarest, F., and Brette, P.*: Presse med. 30: 531, 1922. (3) *Eisele, C. W., and Mason, E. W.*: AM. J. OBST. & GYNEC. 36: 381, 1938. (4) *Flick, L. F.*: Hosp. Progr. 1: 285, 1920. (5) *Hilleboe, H. E.*: Personal communication, 1940. (6) *Ianne, C. F.*: AM. J. OBST. & GYNEC. 38: 448, 1939. (7) *Jameson, E. M.*: Am. Rev. Tuberc. 12: 72, 1930. (8) *Idem*: AM. J. OBST. & GYNEC. 36: 59, 1938. (9) *Jennings, F. L., Mariette, E. S., and Litzenberg, J. C.*: Am. Rev. Tuberc. 25: 687, 1922. (10) *Litzenberg, J. C.*: Minnesota Med. 9: 129, 1926. (11) *Myers, J. A.*: Obstetric Medicine, by Adair and Stieglitz, Sec. II, Chap. VI, 1934. (12) *Myers, J. A.*: J. A. M. A. 112: 1904, 1939. (13) *Rist, E.*: Rev. d. tuberc. d. Uruguay 2: 244, 1921. (14) *Idem*: Brit. M. J. 2: 247, 1927.

520 LA SALLE BUILDING.

PREMATURE ELECTIVE RUPTURE OF THE MEMBRANES

A COMPARATIVE STUDY

W. C. KEETTEL, M.D., A. W. DIDDLE, M.D., AND E. D. PLASS, M.D.,
IOWA CITY, IOWA

(From the Department Obstetrics and Gynecology, University of Iowa)

IN 1936, Plass and Seibert¹ reported on the results obtained in 681 consecutive patients in whom premature rupture of the membranes had been employed as a means for inducing labor, and concluded that this procedure offers the safest and most efficient method for inaugurating parturition. Since the series included 84 patients who presented some complication of pregnancy and since no control material was utilized, the data did not permit a real comparison except in most general terms. Because of the apparent good results, and because of the peculiar conditions in regard to obstetric patients in the University Hospitals, elective premature rupture of the membranes has been employed extensively during the intervening period. The present study was designed to permit an accurate comparison between patients who had late spontaneous rupture of the membranes and those who were subjected to induction of labor by elective early rupture of the bag of waters.

MATERIAL

One thousand consecutive normal parturient women with cephalic presentations and with later spontaneous rupture of the membranes constitute Group I; while a similar number of normal women in whom labor was induced by early elective rupture of the membranes constitute

TABLE IV. THE RELATION OF PARITY TO THE LATENT PERIOD

NUMBER OF PREVIOUS CHILDREN	TOTAL CASES	NO DATA	LABOR LESS THAN ONE HOUR	LATENT PERIOD LABOR 24 HR. AND UP			
				1 TO 5	6 TO 23	NUMBER	PER CENT
0	281	7	161	75	28	10	3.5
1	215	4	131	50	24	6	2.8
2	155	3	97	36	13	6	3.9
3 to 5	237	4	155	46	23	9	3.8
6 or more	112	0	71	17	16	8	7.1
No data	--	--	--	--	--	--	--
Total	1,000	18	615	224	104	39	3.9

The condition of the cervix at the time of rupture of the membranes apparently had a definite effect upon the length of the latent period, as might have been anticipated. Noneffacement of the canal and the absence of preliminary dilatation of the os both predisposed to prolongation of the latent period, but did not invariably postpone the onset of labor. In 59 per cent of the women with uneffaced cervixes and in 60 per cent of those in whom the os was dilated only to admit one finger (not more than 2 cm.), the latent period was less than one hour. On the other hand, 80 per cent of those with latent periods of twenty-four hours or more had uneffaced and undilated cervixes.

The duration of the pregnancy as evidenced by the size of the baby evidently influenced the latent period more than any other factor. Among the 39 women with latent periods of more than twenty-four hours, there were five children (12.8 per cent) weighing less than 2,500 Gm., whereas children of this size represented only 1.8 per cent of those born to mothers having latent periods of under one hour. This relationship was more strikingly shown in a separate series of 130 patients in whom labor was induced by this technique, because of medical indications, and among whom there were 8 latent periods of more than twenty-four hours; three of these children weighed less than 2,500 Gm. (37.5 per cent).

TABLE V. DURATION OF LABOR IN RELATION TO PARITY

GROUP	PARITY	TOTAL IN GROUP	DURATION OF LABOR						
			0-3	3-5	6-11	12-17	18-29	MORE THAN 30 HOURS	
			HOURS	HOURS	HOURS	HOURS	HOURS	NO. CASES	PER CENT
Spontaneous	0	308	10	38	117	82	48	13	4.2
Elective		281	8	39	121	70	30	13	4.6
Spontaneous	i	213	22	55	85	40	9	2	0.9
Elective		215	28	74	70	26	12	5	2.3
Spontaneous	ii	156	24	49	45	21	16	1	0.6
Elective		155	22	54	52	18	4	5	3.2
Spontaneous	iii to v	217	41	63	68	24	16	5	2.3
Elective		237	38	74	78	26	12	9	3.8
Spontaneous	vi and more	106	20	23	39	13	9	2	1.9
Elective		112	19	32	32	14	7	8	7.1
Spontaneous	Total	1000	117	228	354	180	98	23	2.3
Elective	Total	1000	115	273	353	154	65	40	4.0

Duration of Labor.—The total duration of labor (Table V) shows no significant difference in the two groups, except that there was a definite increase in the number of prolonged parturitions (more than thirty hours) among the parous women in Group II. The percentages of prolonged labors in the primigravidas (4.2 per cent and 4.6 per cent, respectively) were practically identical; but in each division of the multigravidas the percentage was appreciably higher, with the difference most

there is no obvious explanation. Prolapse of the cord occurred twice in Group I and four times in Group II, but both babies in the former were lost (100 per cent) whereas there was only one fetal fatality (25 per cent) in the latter. The only maternal death involved a patient in Group I who developed agranulocytosis following arsphenamine therapy for latent syphilis.

Special Data on Group II.—The technique of rupturing the membranes was that previously described¹ except that a small amount of aqueous merthiolate (1:1000) or of mereresin (1:1000) was introduced into the vagina prior to puncture of the bag of waters. No particular effort was made to "strip" the membranes during the procedure. Except in 14 instances, the rupture of the membranes was preceded by medical induction (the Watson technique was employed in 978 patients, and 8 others were given only castor oil and quinine). In certain cases of prolonged latent periods various forms of medication were administered in an attempt to stimulate uterine contractions (castor oil and pituitrin, 1; castor oil and quinine, 2; quinine, 5; quinine and pituitrin, 1; pituitrin, 7; and hot soapsuds enema, 1).

TABLE III. HEIGHT OF PRESENTING PART AT TIME OF ELECTIVE RUPTURE

Floating	27
Fixed above spines	805
Engaged, at spines	134
Engaged, below spines	6
No data	28
Total	1000

The station of the presenting part at the time of elective rupture is presented in Table III. It should be noted that the head was fixed but not engaged in the majority of instances, but was floating in only 27 cases. Effacement of the cervix was complete in 117 cases and partial in 235, while in 618 patients there was no retraction (there were no data on 30 cases). The external os was closed in 15 cases, but was dilated 1 to 2 cm. in 663 and open 2 to 5 cm. in 284 cases (there were no data on 38 patients). In general it is unwise to attempt puncture of the bag of waters when the cervix will not easily admit one finger (1 to 2 cm.).

MATERNAL RESULTS

The available data were analyzed in conformity with the plan employed in the early paper, since it is felt that the factors there considered are perhaps most important in any attempted evaluation. Information on the relative condition of the cervixes after spontaneous and elective membrane rupture was not available because of the impossibility of carrying out follow-up examinations on a clientele which came from all parts of the State. However, the experience gained from routine speculum examinations at the time of discharge from the hospital (eight to ten days after delivery) tends to confirm the observations of others (Schumann²) that "dry labor" does not increase the number or severity of cervical lacerations.

Latent Period.—The period elapsing between the rupture of the membranes and the onset of active, strong labor pains was less than one hour in 615 patients, in many of whom preliminary pains had already appeared as a result of the medical induction. In 224 women, the latent period was one to six hours, in 104 it was six to twenty-four hours, and in 39, there was a delay of more than twenty-four hours (no data are available in 18 instances) (Table IV). The longest latent period, 136 hours, was followed by normal delivery and an afebrile puerperium. In approximately 14 per cent of the patients the latent period was longer than six hours; parity appears to have no particular significance except in the group with six or more previous children, where the percentage is increased by one-half to 21 per cent.

TABLE VIII. POST-PARTUM FEVER IN RELATION TO PARTU, LATENT PERIOD, AND DURATION OF LABOR

GROUP	HIGHEST POST-PARTUM TEMPERATURE	PARTU		DURATION OF LABOR		LATENT PERIOD*	
		NONE	1 OR MORE	0 TO 17 HOURS	18 HOURS OR MORE	0 TO 5 HOURS	6 OR MORE HOURS
Spontaneous Elective	Under 100.4°F.	196	554	669	81	627	99
		177	569	681	65	74.7%	70.0%
Spontaneous Elective	100.4°F. or more	112	138	210	40	212	42
		104	150	214	40	25.3%	30.0%
Total		308	692	879	121	839	141
		281	719	895	105		

*No data on 20 cases.

TABLE IX. FATE OF CHILD IN RELATION TO WEIGHT

BIRTH WEIGHT (GRAMS)	GROUP	TOTAL BIRTHS	STILLBIRTHS						NEONATAL DEATHS							
			INTRA-PARTUM INFECTION	HYDRO-CEPHALIC	ANCE-PHALIC	CON-GENI-TAL SYPH-ILIS	INTRA-CRA-NIAL HEMOR-RHAGE	PREMA-TURITY ATELEC-TASIS AS-PIXYX-IA	PRO-LAPSED CORD AND ARM	NO DATA	MAL-FOR-MA-TIONS	PNEU-MONIA	ANCE-PHALIC	PREMA-TURITY ATELEC-TASIS AS-PIXYX-IA	NO DATA	INTRA-CRA-NIAL HEMOR-RHAGE
Up to 2,500	Spontaneous	51			1	1	1*	1		1	1			5	0	3*
	Elective	20		2						0			1			
Above 2,500	Spontaneous	949					2	2	2	0			1	1	0	2†
	Elective	980	2	1	1		3		1	2	1	2		2	1	
Totals	Spontaneous	1000	2	2	2	1	3	2	2	1	1	2	0	6	0	3
	Elective	1000		1	2	0	3	0	1	2	1	0	0	3	1	2

*Cisternal puncture.

†Clinical diagnosis.

marked in those with the greatest number (six or more) of previous children. On the other hand, labors of less than twelve hours' duration were slightly less common (77.5 per cent) in Group I than in Group II (79.3 per cent). Such data suggest that the birth process tends to be either slightly shortened or somewhat prolonged when labor is induced electively by premature rupture of the membranes, but give no clue as to the factors producing either tendency.

Method of Delivery.—Parturition was spontaneous in 93 per cent of each group, with operative intervention undertaken only for definite indications in the remaining 7 per cent. Among the primigravidas, the operative incidence was above the average, with 15.9 per cent in Group I and 20.3 per cent in Group II. The incidence of the various types of operations is specified in Table X.

Blood Loss.—The average blood loss was 164 c.c. in Group I and 201 c.c. in Group II, but there were more patients (46) in the former group who suffered more or less severe post-partum hemorrhage (more than 600 c.c. blood loss) as against 34 in the latter. This higher incidence of excessive bleeding among the Group I patients was apparent irrespective of the duration of labor (Table VI), and became increasingly noticeable as the length of parturition increased.

TABLE VI. BLOOD LOSS IN RELATION TO LABOR

GROUP	DURATION OF LABOR	TOTAL IN GROUP	BLOOD LOSS			
			LESS THAN 199 C.C.	200 TO 599 C.C.	600 C.C. OR MORE	
					NO. CASES	PER CENT
Spontaneous	0 to 5 hours	345	198	133	14	4.0
Elective		388	216	161	11	3.8
Spontaneous	6 to 17 hours	534	253	259	22	4.3
Elective		507	246	241	20	3.9
Spontaneous	More than 18 hours	121	49	62	10	8.2
Elective		105	51	51	3	2.8
Spontaneous	Total	1000	500	454	46	4.6
Elective		1000	513	453	34	3.4

TABLE VII. BLOOD LOSS IN RELATION TO LATENT PERIOD*

GROUP	LATENT PERIOD	TOTAL GROUP	BLOOD LOSS			
			LESS THAN 199 C.C.	200 TO 599 C.C.	600 C.C. OR MORE	
					NO. CASES	PER CENT
Elective	0 to 1 hour	615	314	279	22	3.6
Elective	1 to 6 hours	224	114	106	4	1.8
Elective	6 to 24 hours	104	61	38	5	4.7
Elective	More than 24 hours	39	18	19	2	5.1
Elective	Total	982	507	442	33	3.4

*No data on latent period in 18 cases.

Prolongation of the latent period in Group II produced some increase in the number of post-partum hemorrhages (Table VII) among those who did not respond within one hour. The lower incidence when the latent period was from one to six hours may well be an artifact dependent upon unknown factors.

Puerperal Morbidity.—The puerperal morbidity rates based upon readings of 100.4° F. or more at any time during the first ten days of the puerperium with temperatures taken every four hours day and night were 25.0 per cent for Group I and 25.4 per cent for Group II (Table VIII). One day fevers were present in 141

DISCUSSION

The results obtained in this series of 1000 inductions of labor by premature artificial rupture of the membranes largely confirm our previous conclusion that this procedure is both efficient and relatively safe, but comparison with an equal number of uninduced labors does not lend support to the belief that labors induced in this fashion differ materially from those which start spontaneously. Certain apparent advantages gained under this type of induced labor are counterbalanced by other evident risks which appear to be connected directly with the technique employed.

Intrapartum infections and prolapses of the cord and arm were twice as frequent in the induced series, and this increase may probably be attributed directly to the procedure. On the other hand the reduced number of post-partum hemorrhages in Group II can scarcely be ascribed to any protective action of the induction technique, since the average blood loss among the entire group of patients was somewhat greater than in Group I and was increased by extension of the latent period beyond six hours.

The effect of early membrane rupture on the duration of labor is not clear-cut and the statistical results are hard to interpret, since there seems to be a tendency both toward shorter average labors and for an increase in the number of unusually prolonged parturitions. Among the primigravidas, the total duration of labor was less than twelve hours in 53.6 and in 59.8 per cent, respectively, in Groups I and II, but there was a slightly higher percentage of prolonged labors (4.6 per cent) in Group II than in Group I. On the other hand, 77.2 per cent and 79.7 per cent of the multigravidous labors were completed in less than twelve hours in Group I and II, respectively; whereas labors of more than thirty hours' duration were more than two and one-half times as common (3.7 per cent) in Group II as in Group I (1.4 per cent), a fact which does not correlate with the lower incidence of post-partum hemorrhage in the former.

The fact that 25 per cent of the patients in each group had post-partum temperature elevations to 100.4° F. or above may seem excessive, but it must be recalled that temperatures were taken every four hours day and night and that one-half to two-thirds of these fevers were without clinical significance, in that they disappeared spontaneously in less than twenty-four hours. The incidence of true puerperal morbidity, as represented by the presence of fever for more than one day, was slightly higher in the induced series, and may be explained by the inevitable vaginal manipulations. There were, however, no serious infections and persistent fevers were practically as common in one group as in the other.

The lower fetal death rate in the induced group has already been explained on the basis of the smaller number of premature infants incident to the method of selecting patients for induction. It is interesting that only one infant was lost because of prolapsed cord in Group II as against two in Group I; obviously this is merely a coincidence. The data suggest that intracranial hemorrhage is less frequent among mature infants when the membranes are allowed to rupture spontaneously, but

patients in Group I, leaving a true morbidity rate of 10.9 per cent, and in 120 patients in Group II, making an actual morbidity rate of 13.4 per cent. Twelve patients (1.2 per cent) in Group I and 15 (1.5 per cent) in Group II had fevers which persisted for seven days or longer. None of the infections threatened life and there was only one death in the 2,000 cases, as already mentioned. Primiparity, prolongation of the latent period, and prolonged labor were associated with definite increase in the incidence of febrile reactions.

Fetal Results.—There were 13 (1.3 per cent) stillbirths and 12 (1.2 per cent) neonatal deaths, for a total fetal mortality of 2.5 per cent in Group I, as against 11 (1.1 per cent) stillbirths and 7 (0.7 per cent) neonatal deaths for a total fetal loss of 1.8 per cent in Group II (Table IX). Such data, however, offer an inaccurate means of comparison, since Group I contained 51 babies weighing less than 2,500 Gm., whereas there were only 20 such premature infants in Group II, where every effort was made to insure the maturity of the child before proceeding to the induction. There were 5 stillbirths and 9 neonatal deaths among the prematures in Group I, a total mortality of 27.4 per cent, as against 2 stillbirths and 1 neonatal death among the premature children in Group II, a total loss of 15 per cent.

Considering only the mature infants, there was a mortality rate of 1.1 per cent in Group I and of 1.5 per cent in Group II, the difference being largely explained by the higher incidence (5 to 2) of intracranial hemorrhage and the lower frequency of congenital malformation (2 to 3) in Group II as compared with Group I.

In Group I there were two cases of prolapsed cord, both in vertex presentations, when delivery was effected by midforceps and resulted in stillborn children. One prolapsed arm was treated without radical intervention and the child survived. Group II showed four prolapsed cords and an equal number of prolapsed arms. Two patients with funic prolapse were delivered by podalic version and extraction and 2 by forceps; the single fetal death occurred during forceps delivery. Among the 4 prolapsed arms, 2 were delivered by version and extraction, 1 by forceps and 1 spontaneously. The lone fatality occurred in 1 of the patients delivered by version. In each group, there were 2 fetal deaths associated with prolapse of the cord or an extremity, even though these complications were almost three times as common in patients subjected to elective rupture of the membranes.

In Group II, the fetal risk increased from 0.8 per cent (5 among 615) in those with a latent period of less than one hour to 11.3 per cent (4 among 39) when the onset of labor was delayed more than twenty-four hours.

In both groups, prolongation of the birth process was associated with an increased fetal fatality rate. When delivery occurred within six hours of the onset of labor, the mortality rates were 2.0 per cent in Group I and 0.8 per cent in Group II; with labors lasting six to eighteen hours, the values were 3.1 per cent and 1.9 per cent; and when delivery occurred only after more than eighteen hours, the rates were 5.0 and 5.8 per cent, respectively.

Among primigravidas the fetal loss was higher (Group I, 3.9 per cent; Group II, 2.1 per cent) than in those women who had previously borne one or more children (Group I, 1.9 per cent; Group II, 1.7 per cent).

TABLE X. METHOD OF DELIVERY IN RELATION TO FATE OF CHILD

METHOD OF DELIVERY	DISCHARGED ALIVE	STILLBIRTHS	NEONATAL DEATHS	TOTALS
Series I				
Spontaneous	912	9	9	930
Low forceps	58	0	3	61
Midforceps	4	2	0	6
Version	1	1	0	2
Craniotomy	0	1	0	1
Series II				
Spontaneous	915	9	7	931
Low forceps	58	1	0	59
Midforceps	5	1	0	6
Version	3	1	0	4

gestation. They state that "it is not an unduly dangerous procedure," and that "the finding of intact decidua without chorionic villi is strong presumptive evidence of extrauterine pregnancy. The absence of decidual reaction is not reliable evidence against ectopic pregnancy." They found, as did others before them, that the presence or absence of decidua is determined by the duration of the uterine bleeding. In our series we find that not only the duration, but also the amount of bleeding, is an important factor.

Siddall and Jarvis charted the relationship of the duration of the bleeding to the presence or absence of decidua, and they collected other reports from the literature. In Table I we have added our own findings to those charted by Siddall and Jarvis. Judging by the small number of cases reported, curettage is not frequently employed in ectopic pregnancy. Siddall found uterine decidua in every case in which the bleeding, irrespective of the amount, lasted ten days or less. In our series of 32 cases there are 5 patients that bled ten days or less (including 2 who had no history of bleeding), and all 5 showed decidua in the uterus. Three patients bled for two weeks, and two of these showed decidua.

TABLE I. SIX SERIES OF EXTRAUTERINE PREGNANCIES SHOWING INCIDENCE OF DECIDUA ACCORDING TO ONSET OF ABNORMAL BLEEDING BEFORE ENDOMETRIUM WAS OBTAINED (ADAPTED FROM SIDDALL AND JARVIS)

ONSET OF ABNORMAL BLEEDING BEFORE SPECIMEN WAS SECURED	SERIES	CASES	DECIDUA	PERCENTAGE
None to one week	Sampson	2	2	100.0
	Geist and Matus	11	10	90.9
	Moritz and Douglas	12	2	16.7
	Boerner	11	10	90.9
	Siddall and Jarvis	7	7	100.0
	Bellevue Hospital	4	4	100.0
	Total	47	35	74.5
Eight days to two weeks	Sampson	3	1	33.3
	Geist and Matus	12	7	58.3
	Moritz and Douglas	11	2	18.2
	Boerner	4	1	25.0
	Siddall and Jarvis	8	6	75.0
	Bellevue Hospital	4	3	75.0
	Total	42	20	47.6
Fifteen days to three weeks	Sampson	1	0	00.0
	Geist and Matus	6	2	33.3
	Moritz and Douglas	6	1	16.7
	Boerner	7	2	28.6
	Siddall and Jarvis	3	2	66.7
	Bellevue Hospital	5	4	80.0
	Total	28	11	39.3
Twenty-two days to four weeks	Sampson	8	2	25.0
	Geist and Matus	4	2	50.0
	Moritz and Douglas	12	1	8.3
	Boerner	4	1	25.0
	Siddall and Jarvis	8	3	37.5
	Bellevue Hospital	6	0	00.0
	Total	42	9	21.4
Twenty-nine days to twelve weeks	Sampson	11	0	00.0
	Geist and Matus	6	2	33.3
	Moritz and Douglas	12	2	16.7
	Boerner	4	0	00.0
	Siddall and Jarvis	12	4	33.3
	Bellevue Hospital	13	3	23.1
	Total	58	11	18.9
	All cases	217	86	39.6

the size of the series does not permit such a conclusion, since several of the children were not subjected to autopsy.

CONCLUSIONS

The induction of labor by premature artificial rupture of the membranes does not significantly alter the birth process or affect the prognosis for the mother or her child.

REFERENCES

- (1) Plass, E. D., and Seibert, C. W.: AM. J. OBST. & GYN. 32: 785, 1936.
- (2) Schumann, E. A.: AM. J. OBST. & GYN. 32: 793, 1936.

CORRELATION OF FRIEDMAN TEST AND PHASE OF ENDOMETRIUM IN ECTOPIC PREGNANCY

MYRON E. GOLDBLATT, M.D., F.A.C.S., AND HAROLD A. SCHWARTZ,
A.B., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine, and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division, Bellevue Hospital)

THE diagnosis of a recently ruptured ectopic gestation with profuse intra-abdominal hemorrhage is usually not difficult. It is the unruptured extrauterine pregnancy or one with slight or recurrent internal bleeding that taxes one's diagnostic acumen. Here the history, physical examination, and routine laboratory procedures are frequently inadequate to establish the diagnosis. These findings must often be supplemented by the Aschheim-Zondek test (or Friedman modification), uterine curettage, peritoneoscopy, cul-de-sac aspiration, posterior colpotomy, and occasionally an exploratory laparotomy. One should resort to any feasible and practical test or procedure in order to avoid an unnecessary abdominal operation. With these facts in mind, the writers believed that it would be of value to study the type of endometrium, the result of the Friedman test, the condition of the placental tissue of the excised salpinx, and the correlation of the data thus obtained with the clinical picture.

For the purpose of this study, the cases of patients with ectopic pregnancy entering the Gynecologic Service of the Bellevue Hospital from June, 1934, to December, 1939, inclusive, were reviewed. At Bellevue Hospital extrauterine pregnancy is not an uncommon finding, and during this five-and-one-half-year period there were 193 such diagnoses, confirmed by operation. Because, however, many of these patients presented the picture of hemorrhagic shock and required as short a surgical procedure as possible, and because curettage as a diagnostic aid in ectopic pregnancy was seldom used until relatively recently, all the desired data could be secured on only 32 patients. It is from these 32 cases with complete data that our information was obtained (see Table II).

Siddall and Jarvis in a review of 38 cases from the Harper Hospital at Detroit concluded that uterine curettage is very valuable as a diagnostic aid in ectopic

not be influenced in the use of terms. Two patients had no history of bleeding, 17 bled scantily, and 13 bled moderately or profusely. Both of those with no bleeding had decidua. The 17 with scanty bleeding bled from one day to twelve weeks, and 12 (63 per cent) of these had decidua; adding the two with no bleeding to this series, 14 of the 19 patients (74 per cent) with scanty or no bleeding, irrespective of the duration of the bleeding, had decidua. The 13 patients with moderate or profuse bleeding bled from two to ten weeks, and only 2 (15 per cent) had decidua. Of these two, one bled moderately for three weeks and one profusely for three weeks, both thus bleeding a relatively short period of time.

As mentioned earlier, of 19 patients that bled longer than three weeks, only 3 had decidua. In all three the bleeding was only scanty in amount (see Table II). Hence, no patient who bled more than scantily for more than a period of three weeks still showed decidua. It appears therefore that any patient with an ectopic pregnancy who bleeds only scantily, regardless of the duration of the bleeding, may still have decidua, but with a decreased expectancy for decidua, as the duration of the bleeding increases; and that any patient who bleeds moderately or profusely for more than three weeks is extremely likely not to have decidua. The expectancy of decidua appears to be inversely proportional to the total amount of blood lost per vaginam, the less the blood loss, the greater the chance for decidua being present. Consequently, a patient that bleeds scantily for a certain duration of time is much more likely to have decidua than is the patient who bleeds moderately or profusely for the same period of time.

Of the 32 ectopic pregnancies studied, 24 had a positive and 8 a negative Friedman test. No patient with a negative Friedman test had decidua. No patient with decidua had a negative Friedman test. While the presence of decidua required a positive Friedman reaction in every case, a positive Friedman test did not guarantee the presence of decidua. Of the 24 patients with positive Friedman, 14 had decidua and 10 did not. According to an earlier conclusion, in the 10 cases without decidua one would expect either a long period of scanty or more bleeding, or a relatively short period with moderate or profuse bleeding. This is true except for one patient who bled for two weeks and only scantily (Case 15 of Table II); of the remaining 9 patients without decidua, 8 bled four weeks or longer, and one bled moderately for three weeks. Here again one sees the importance of the amount as well as the duration of bleeding in predicting the presence or absence of uterine decidua.

An attempt was made, by microscopic examination of the Fallopian tube, to correlate the state of degeneration or preservation of the placental tissue in the tube with the actual Friedman test. The authors do not agree with Kaplun, who states that there is no parallelism between the morphologic activity of the trophoblast and the outcome of the Aschheim-Zondek reaction. For the purpose of this study, the placental tissue was graded according to its degree of degeneration as 0, slight, moderate, and marked degeneration (see Table II). The actual result of the Friedman test was not known at the time of the grading of the degree of degeneration and the recording of the probable result of the rabbit test.

In the cases designated a 0 placental degeneration, the placental tissue was in perfect condition; the villi showed no fibrosis, and they contained blood vessels which contained erythrocytes. In these patients it was felt that the Friedman test should be positive. There were 7 such patients. In all 7 the actual Friedman test was positive. In only 4, however, was decidua present in the uterus, the other 3 uteri containing a proliferating endometrium. In one case decidua was present on the surface of the ovary even though it was absent inside the uterus (see Fig. 1, A, B, C).

Thus, of 8 cases that bled two weeks or less, 7 (85 per cent) had uterine decidua. Five patients bled from two to three weeks, and 4 (80 per cent) showed decidua. Of 6 patients that bled three to four weeks none showed decidua, but of 19 patients who bled four to twelve weeks, inclusive, 3 (16 per cent) contained decidua. Expressing these facts in another way, of 13 patients who bled three weeks or less, 11 (85 per cent) showed decidua, and of 19 patients who bled from twenty-two days to twelve weeks, only 3 (16 per cent) had decidua.

Of the 32 cases studied, 14 had decidua. Of the 14 with decidua all bled only scantily or not at all, except for one. This one bled moderately for three weeks. Another patient, however, bled scantily for twelve weeks, and the uterus still contained decidua. No other patient of the 32 bled this long. Hence, it immediately appears that the amount of uterine bleeding, as well as the duration, is important in predicting the presence or absence of uterine decidua in ectopic pregnancy.

For the purpose of this paper, the amount of bleeding was described as scanty (including spotting), moderate, or profuse. Naturally, these terms are relative, but they were charted before the study of the endometrium was made and were never again seen until this paper was in preparation, so that the authors could

TABLE II. BELLEVUE HOSPITAL CASES OF ECTOPIC PREGNANCY SHOWING RELATIONSHIP BETWEEN DURATION AND AMOUNT OF VAGINAL BLEEDING, TYPE OF ENDOMETRIUM, RESULT OF FRIEDMAN TEST AND DEGREE OF DEGENERATION OF PLACENTAL TISSUE

NO.	LAST MENSTRUAL PERIOD. WEEKS BE- FORE SPECI- MEN WAS OBTAINED	ONSET OF VAGINAL BLEEDING. WEEKS BE- FORE SPECI- MEN WAS OBTAINED	TYPE OF BLEEDING. SCANT, MODERATE OR PROFUSE	ENDOMETRIUM. PHASE	FRIEDMAN TEST RESULT	PLACENTAL TISSUE. DEGREE OF DEGENERA- TION
1	13	0	0	Decidua	Positive	Slight
2	9	0	0	Decidua	Positive	None
3	5	$\frac{1}{4}$	Scant	Decidua	Positive	Slight
4	8	$\frac{3}{4}$	Scant	Decidua	Positive	Slight
5	8	$1\frac{1}{2}$	Scant	Decidua	Positive	None
6	6	2	Scant	Decidua	Positive	Slight
7	3	2	Scant	Decidua	Positive	Slight
8	4	3	Scant	Decidua	Positive	None
9	8	3	Scant	Decidua	Positive	Slight
10	13	3	Moderate	Decidua	Positive	Insufficient
11	11	3	Profuse	Decidua	Positive	Slight
12	11	6	Scant	Decidua	Positive	Slight
13	8	8	Scant	Decidua	Positive	None
14	12	12	Scant	Decidua	Positive	Slight
15	8	2	Scant	Proliferating	Positive	Slight
16	3	3	Moderate	Proliferating	Positive	None
17	4	4	Moderate	Proliferating	Negative	Slight
18	8	4	Moderate	Proliferating	Positive	Slight
19	8	4	Moderate	Proliferating	Positive	Slight
20	9	4	Moderate	Proliferating	Positive	None
21	11	4	Profuse	Proliferating	Negative	Moderate
22	7	5	Scant	Proliferating	Positive	Slight
23	6	6	Scant	Proliferating	Negative	Moderate
24	7	7	Scant	Proliferating	Positive	None
25	13	7	Moderate	Proliferating	Positive	Marked
26	13	8	Moderate	Proliferating	Positive	Moderate
27	9	9	Scant	Proliferating	Negative	Marked
28	13	10	Moderate	Proliferating	Negative	Marked
29	8	4	Scant	Secretory	Positive	Slight
30	9	6	Scant	Secretory	Negative	Moderate
31	10	6	Moderate	Secretory	Negative	Marked
32	10	6	Moderate	Secretory	Negative	Marked

In the cases designated as slight placental degeneration, many chorionic villi were perfectly preserved or slightly fibrotic, while others were markedly degenerated. Here it was felt that the Friedman test should be positive. There were 15 such patients, and the



Fig. 2A.



Fig. 2B.

Fig. 2A.—A combination of well-preserved and markedly degenerated placental tissue. For the purpose of our classification this was considered "slight" degeneration and was almost always associated with a positive Friedman test and usually with uterine decidua.

Fig. 2B.—Uterine decidua in ectopic pregnancy, obtained by curettage. Same patient as Fig. 2, A. Decidua was never present in the uterus if the placental tissue was more than "slightly" degenerated.



Fig. 3.—Markedly degenerated chorionic villi in the Fallopian tube with an occasional small island of well-preserved syncytial and Langhans cells. In our classification this degeneration was considered "moderate" in amount. In such cases it is believed that the Friedman test cannot be safely predicted. It was negative, however, in three out of four such cases. Decidua was always absent with this degree of placental degeneration.



Fig. 1A.

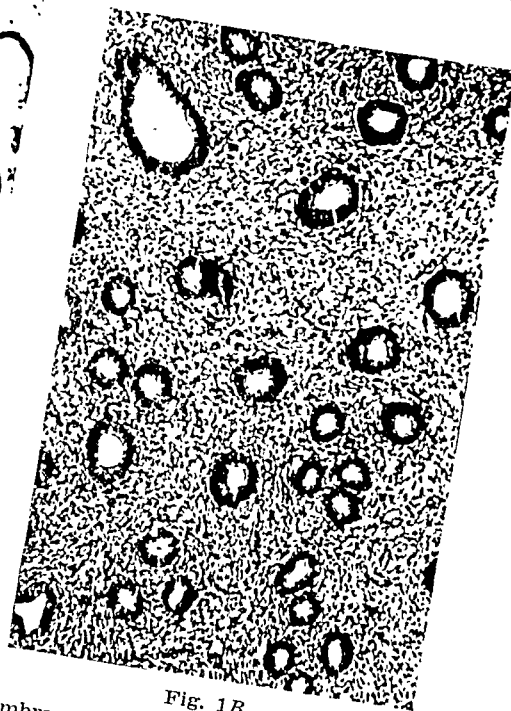


Fig. 1B.

Fig. 1A.—Perfect placental tissue and membranes in the Fallopian tube. The chorionic villi show no evidence of degeneration. While such well-preserved placental tissue is usually associated with uterine decidual. Undegenerated placental tissue, as here pictured, was always associated with a positive Friedman test.

Fig. 1B.—Proliferating endometrium obtained by curettage in an ectopic pregnancy. Same patient as Fig. 1, A. Proliferating endometrium in the uterus is usually associated with moderately or markedly degenerated placental tissue in the tube, but in this case the placental tissue showed no evidence of degeneration.



Fig. 1C.—Decidua on the surface of the ovary, a frequent finding in tubal pregnancy. Same patient as Figs. 1, A and B. In this patient decidua was absent in the uterus even though it was present on the ovary. This means that factors other than placental degeneration may also be important in causing degeneration or extrusion of uterine decidua.

several weeks. Had more microscopic sections through the placental tissue been taken, we believe that our results might have been even more accurate. At any rate, our results indicate a close but not perfect relationship between the state of preservation of the chorionic tissue and the outcome of the Friedman test.

As already noted, the state of preservation of the placental tissue is not always directly related to the presence of uterine decidua. Morphologically perfect placental tissue may be present in the Fallopian tube, and yet decidua may be absent in the uterus, even though decidua be present on the surface of the ovary. On the other hand, uterine decidua may persist in spite of the fact that many chorionic villi may be degenerated. Whenever, in our series, all of the tubal placental tissue was markedly degenerated, uterine decidua was always absent. Long ago Watson showed that the death of the embryo is followed by degeneration of the placenta. It is believed that a decrease in the production of the chorionic and corpus luteum hormones causes the degeneration of the decidua and its expulsion from the uterus, and no doubt this is true. There must, however, be other factors involved in order to explain the discrepancy that may exist between the state of preservation of the placental tissue in the tube and the presence or absence of decidua in the uterus. Among these factors may be included: the suddenness or rapidity with which the placental tissue degenerates or becomes isolated by clot and fibrin from the maternal circulation. It is also conceivable that a hyper-irritable uterus might expel a decidual cast without any appreciable degeneration of placental tissue while a uterus of lower sensitivity might require considerable degeneration of placental tissue before the decidua disappears.

In the three patients with perfect chorionic villi and no uterine decidua, one might wonder whether the decidua actually developed. Judging, however, by the relatively excessive amount of bleeding per vaginam, the decidua probably had been present and had been extruded from the uterus. Moritz and Douglas reported 6 cases without decidua in which there was no history of bleeding or desquamation from the vagina, but we have seen no such cases, and their occurrence, though possible, must be exceedingly rare.

Of the 32 cases studied, 3 patients were operated upon on the day of admission and 8 within one week; 17 were observed from one to two weeks, and 4 from two to nine weeks before operation was performed. Although there is no expectant treatment for ectopic pregnancy, if the diagnosis is established, it would nevertheless appear that the degenerative type of extrauterine gestation can be observed in the hospital with comparative safety for a reasonable period of time until the diagnosis is made. For there were no deaths in this series, and no serious sequelae followed even prolonged observations. All 32 patients were discharged within fifteen days after operation except for one who developed a rather superficial wound infection and remained in the hospital an additional week. We agree with Siddall and Jarvis that a proper curettage in ectopic pregnancy is not deleterious.

Friedman test was actually positive in 14. In 10 the uterus contained decidua while in 5 it was absent (see Fig. 2, A, B).

Those placental tissues designated as marked degeneration consisted chiefly of shadow villi. With this degree of degeneration it was felt that the Friedman test should be negative. There were 5 such cases. In 4 the actual Friedman test was negative. In none of the 5 patients was decidua present in the uterus (see Fig. 4, A, B).



Fig. 4A.



Fig. 4B.

Fig. 4A.—Markedly degenerated shadow villi in the Fallopian tube with no evidence of active chorionic cells. Such placental tissue was considered "markedly" degenerated. In these cases it is felt that the Friedman test should be negative, and this was true in four out of five patients. When the tubal placental tissue was "markedly" degenerated, decidua was always absent in the uterus. In this patient the endometrium was in the early secretory stage.

Fig. 4B.—Early secretory endometrium. Same patient as Fig. 4A. Proliferating endometrium was more commonly found than secretory in the presence of degenerating ectopic pregnancies. The presence or absence of uterine decidua is related to the amount of blood lost per vaginam, the greater the blood loss, the less the chance for decidua to be present.

In the placental tissue designated as moderately degenerated, the chorionic villi were in a stage of degeneration between those designated as slightly and those designated as markedly degenerated. Here, for the most part, the chorionic villi were markedly degenerated, but there were occasional small groups of syncytial or Langhans cells that appeared viable. In this group of cases, the expected Friedman test was recorded as doubtful, for it was felt that a reasonably accurate prediction on the outcome of the biologic reaction could not be made. There were 4 such cases. In 3 the actual Friedman test was negative and in one positive. In all 4, decidua was absent in the uterus (see Fig. 3).

In all of the cases except two, the Friedman test was performed within a few days prior to operation; in these 2 cases (Cases 28 and 30 in Table II) misled by a negative Friedman test, laparotomy was delayed

SUMMARY

1. Thirty-two cases of ectopic pregnancy with complete clinical and laboratory findings are analyzed with regard to the findings on curettage, the result of the Friedman test, the microscopic examination of the removed tube, and the clinical picture.

2. Any patient with an ectopic pregnancy who bleeds scantily, even for many weeks, may still have uterine decidua, but with a decreased decidual expectancy as the duration of the bleeding increases. If the bleeding has been moderate or profuse for more than three weeks, decidua is extremely likely to be absent. The probable presence of uterine decidua is inversely proportional to the total amount of blood lost per vaginam, the less the blood loss, the greater the chance for decidua to be present.

3. No patient with a negative Friedman test had uterine decidua at the time of curettage. No patient with uterine decidua had a negative Friedman test.

4. There is a close but not perfect relationship between the result of the Friedman test and the state of preservation of the chorionic villi.

5. Occasionally one finds morphologically perfect placental tissue in the Fallopian tube, a positive Friedman test, and an absence of decidua in the uterus. Such patients always had a history of prolonged or profuse bleeding per vaginam.

6. Factors other than placental degeneration are probably important in causing decidual degeneration and expulsion. Among such factors may be the suddenness of placental degeneration, and the sensitivity and irritability of the decidua or myometrium.

7. In a well-regulated hospital, a suspected case of ectopic pregnancy without acute symptoms may be observed with comparative safety for rather prolonged periods of time until the diagnosis is made. Seventeen patients were observed from one to two weeks and 4 patients still longer, without serious sequelae.

8. If while under observation for several days or longer the patient's course has been febrile, the uterus appears less likely to contain decidua than if the temperature had remained normal.

9. In cases of suspected old ectopic pregnancy where the Friedman test is negative, aspiration of the cul-de-sac may confirm the diagnosis. Here curettage would reveal no decidua, but may nevertheless be indicated to rule out the presence of an old incomplete abortion or placental polyp.

REFERENCES

- Siddall, R. S.*: AM. J. OBST. & GYN. 31: 420, 1936. *Siddall, R. S., and Jarvis, C.*: Surg. Gynec. Obst. 65: 820, 1937. *Moritz, A. R., and Douglas, M.*: Ibid. 47: 785, 1928. *Kaplun, E. M.*: Zentralbl. f. Gynäk. 58: 1826, 1934. *Watson, B. P.*: Scottish M. & S. J., January, 1906.

The admission temperature is of no value in predicting the presence or absence of decidua in ectopic pregnancy.

On admission 23 patients had a normal temperature and 10 of them had decidua at the time of curettage, an incidence of 43.5 per cent. Nine patients had an admission temperature of 100° to 102° F., and 4 of these had decidua, an incidence of 44.4 per cent. If, however, a patient is observed for a period of five or more days, it appears from a small series of cases that the presence of a persistently normal temperature is a slight point in favor for, and fever a point against, the finding of decidua. Of 14 patients with a normal temperature during such a period of observation, 6 (43 per cent) had decidua, whereas of 9 with a fever up to 101° only 2 (22 per cent) showed decidua.

Of the 32 patients studied only 8 had 400 c.c. or more blood in the peritoneal cavity at the time of operation. In six of these the correct diagnosis was made within a week and laparotomy promptly performed. These constitute the more acute ectopics of this series, and four of them were interstitial pregnancies. In two patients with 400 c.c. or more blood in the peritoneal cavity, the correct diagnosis was missed, due chiefly to reliance on a negative Friedman test, one patient being observed in the hospital for four weeks and one for nine weeks before operation was performed. In these two patients aspiration of the cul-de-sac might have established the diagnosis and shortened the period of observation. Where an ectopic gestation is strongly suspected, even in the presence of a negative Friedman test, aspiration of the cul-de-sac would appear to be indicated. In such cases with a negative Friedman, curettage would show no decidua, but nevertheless might be of value to rule out an old incomplete abortion or placental polyp.

Studies were also made of the leucocytic count of the blood and of the erythrocytic sedimentation rate. They were absolutely of no value in predicting the state of degeneration of the placental tissue, the outcome of the Friedman test, or the presence or absence of decidua.

It is often stated that a previous attack of salpingitis predisposes to the occurrence of an ectopic pregnancy. Microscopic examination of the tube containing the gestation is often of disputed value in proving the presence or absence of a previous infection in that tube, due to the distortion of the plicae and leucocytic infiltration that may accompany a tubal pregnancy. In our series, however, laparotomy revealed in 20 of the 32 patients incontestable gross evidence of a previous inflammation of the tube not containing the pregnancy, such evidence being clubbing of the tube, closure of the fimbriated extremity, or marked peritoneal adhesions about the tube. Four patients of the series had had a previous tubal pregnancy on the opposite side with the removal of the involved salpinx.

The simultaneous occurrence of a tubal and intrauterine gestation has often been reported. In one of our cases of ampullary tubal pregnancy with internal rupture, chorionic villi were found in the uterine cavity as well as in the salpinx. In this particular case, we do not believe that two pregnancies existed but that chorionic villi were extruded from the tubal lumen into the uterine cavity, for the placental tissue in the uterus appears entirely unrelated and unattached to the decidua. Regardless of the explanation, it should be remembered that very occasionally placental tissue can exist simultaneously in both the tubal and uterine lumina.

VAGINAL SMEARS

The vaginal smears were prepared according to the method described in previous communications.^{11, 20} In 15 patients there was evidence of a moderate estrogen deficiency in the vaginal smear, as manifested by the presence of a few small deep "atrophy" epithelial cells and leucocytes. In 11 patients the vaginal smears exhibited many "atrophy" epithelial cells and leucocytes, indicative of an advanced estrogen deficiency (Fig. 1). The vaginal smears of the remaining 19 patients fell into the borderline group and could not be classified definitely as showing estrogen deficiency or evidence of full estrogen effect.

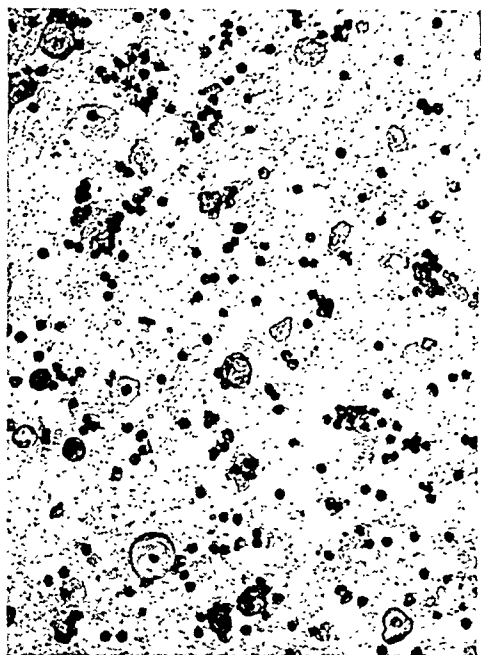


Fig. 1.



Fig. 2.

Fig. 1.—Case L. W. (Aged 53 years; four years postmenopause.) Preliminary smear indicative of advanced estrogen deficiency. Note "atrophy" cells and leucocytes.

Fig. 2.—Case L. W. Vaginal smear following the administration of 5 mg. of stilbestrol over a period of four days. Note the large, squamous cells with indistinct small nuclei and absence of leucocytes and "atrophy" cells.

Signs of an estrogenic effect, characterized by the increase in size and number of the large, squamous, epithelial cells and a diminution in the number of leucocytes and deep "atrophy" cells, were noted as early as four days following the administration of stilbestrol. Doses of 5 to 10 mg., given over a period of four to ten days, were sufficient to induce a full estrogenic smear characterized by the absence of leucocytes and deep "atrophy" cells (Fig. 2) and the predominance of large squamous cells with very small nuclei. Smears indicative of a full estrogenic effect persisted while stilbestrol was being administered. Following the discontinuation of treatment, the vaginal smears began to show signs of regression to their former deficiency state within fifteen to twenty days.

VAGINAL MUCOSA

Vaginal biopsy studies were made on a group of 11 biopsies taken from 5 different patients. In each case, definite morphologic changes, indicative of a strong estrogen effect, were induced following the administration of stilbestrol. Fig. 3 shows a preliminary vaginal biopsy, obtained from Case S. R., characterized by a narrow epithelial layer, consisting chiefly of a basilar zone (5 to 6 cell

EVALUATION OF STILBESTROL AS A THERAPEUTIC ESTROGEN

U. J. SALMON, M.D., S. H. GEIST, M.D., AND R. I. WALTER, M.D.,
NEW YORK, N. Y.

(From the Gynecological Service and the Laboratories of the Mount Sinai Hospital)

IN 1938, Dodds and his co-workers^{1, 2} reported the synthesis of 4:4' dihydroxy- α : β -diethyl stilbene, a compound unrelated chemically to natural estrogens which, however, possesses estrogenic properties. The following year, numerous clinical reports^{3-10, 16-19} attested to the fact that, in the human being, stilbestrol was capable of relieving menopausal symptoms. However, a number of the patients developed toxic symptoms, the incidence of which seemed to vary considerably in the various series of cases reported. In a preliminary report,⁶ presented before the New York State Medical Society, in April, 1939, we stated that the high incidence of toxic symptoms, which accompany the use of stilbestrol, constituted a serious objection to its use clinically. In this communication, we wish to report in detail the results of our further experience with stilbestrol, supplemented by morphologic studies of the endometrium, vaginal mucosa, and gonadotropic hormone assays.

MATERIAL

This study was conducted on a group of 45 patients and includes the series reported in the preliminary communication. The patients varied in age from 24 to 72 years. The duration of the menopause varied from six months to nineteen years. There were 22 spontaneous postmenopausal patients, 9 surgical castrates, 6 x-ray castrates, and 8 patients who were still menstruating but who had menopausal symptoms. The symptoms varied considerably in nature and intensity. The most common symptom was flushes, which were present in 39 patients. The other symptoms noted were headache in 7; vaginal pruritus in 7; vertigo in 8; weakness in 6; arthralgias in 4; urinary symptoms in 2; insomnia in 3; and vaginitis and dyspareunia in 2.

DOSAGE

Diethyl stilbestrol* was administered orally and intramuscularly in varying doses. The oral dose varied from 0.3 mg. to 6 mg. daily, and the intramuscular dose varied from 1 to 5 mg., given from 1 to 3 times weekly. The total dosage varied from 7 mg. to 424 mg. The patient who received the largest total dose was treated over a period of five months. The longest duration of treatment was nine months in one patient who received a total of 177 mg.

In the evaluation of the efficacy of stilbestrol as a therapeutic agent, it was felt desirable to employ objective criteria of its action in addition to clinical evidence of improvement. The objective criteria employed were: vaginal smears, vaginal biopsies, endometrial biopsies and gonadotropic hormone studies.

*For the stilbestrol used in this investigation, we are indebted to Mr. J. Hutchinson, Ayerst, McKenna and Harrison, Rouses Point, N. Y. and to Dr. J. A. Morrell, E. R. Squibb and Sons, New York City.

recurred. In no instance was the bleeding sufficiently severe to be of serious consequence. Nevertheless, the stilbestrol was usually discontinued with the onset of bleeding.

In most cases, the bleeding occurred during the period of stilbestrol administration. There is apparently a wide variation in the dosage necessary to induce uterine bleeding. In this series, as noted above, the dose varied from 20 mg. to 228 mg. and, in other patients, doses of comparable and larger magnitude did not induce uterine bleeding.



Fig. 5.—Case S. R. Preliminary atrophic endometrium.



Fig. 6.—Case S. R. Endometrial biopsy following 20 mg. of stilbestrol, intramuscularly, showing slight proliferative changes.

Eleven endometrial biopsies were taken on 6 different patients. In each of them, various degrees of proliferation were induced, varying from slight to advanced proliferation resembling hyperplasia. These effects were produced with stilbestrol administered both orally and intramuscularly. Four of the endometrial biopsies were taken during periods of bleeding. There is, apparently, no relationship be-

layers thick) and the absence of a cornified and vacuolated zone. In addition, there is considerable round cell and leucocytic infiltration of the intraepithelial and subepithelial zones, characteristic of chronic and subacute senile vaginitis.

Following the intramuscular injection of 20 mg. of stilbestrol in two days, a biopsy on the fifth day revealed a tremendous increase in thickness of the epithelium, due chiefly to the appearance of a wide vacuolated zone and increased cellularity of the basalis. In addition, there was a downgrowth of the papillae and a disappearance of leucocytes (Fig. 4).

In another patient (O. W.), a vaginal biopsy taken following the administration of 113 mg. of stilbestrol over a period of seven months revealed a mucosa of normal thickness, a well-defined cornified zone and intraepithelial zone and a normal basalis. There was no evidence of abnormal cellular proliferation.



Fig. 3.



Fig. 4.

Fig. 3.—Case S. R. (Aged 60 years; twelve years postmenopause.) Preliminary vaginal biopsy, showing moderate degree of atrophy. Note the narrow epithelial layer; absence of cornified and vacuolated zones; presence of subepithelial and intraepithelial round cell infiltration.

Fig. 4.—Case S. R. Vaginal biopsy following 20 mg. of stilbestrol administered intramuscularly over a period of two days. Note the wide vacuolated zone and increased cellularity and proliferative activity of the basalis.

ENDOMETRIUM

Uterine bleeding is not uncommon following the administration of naturally occurring estrogens. In this series of cases, uterine bleeding occurred 5 times in 4 different patients. The smallest amount of stilbestrol which induced uterine bleeding was 20 mg., given intramuscularly. This occurred in a 52-year-old patient (natural menopause, six years), who was given 10 mg. of stilbestrol in 2 successive days. On the third morning, uterine bleeding began and lasted six days.

In another patient, bleeding of four days' duration occurred following the administration of 228 mg. of stilbestrol, given orally, over a period of two and one-half months. Bleeding then stopped for seven days. Following the re-administration of 12 mg. of stilbestrol, orally, over a period of three days, bleeding

GONADOTROPIC HORMONE STUDIES

It has previously been demonstrated that the excessive production of castrate gonadotropic factor in the menopause can be inhibited by the administration of adequate amounts of estrogens.¹²⁻¹⁴ Gonadotropic hormone studies were performed on 8 menopause patients in this series to determine whether stilbestrol could inhibit the excessive production of gonadotropic hormone by the pituitary. A modification of the alcohol-acetone precipitation method was employed for the extraction of the castrate gonadotropic factors from the urine.¹⁵ Hormone studies were discontinued in 3 of the patients because they developed severe toxic symptoms. In only one of the remaining 5 patients did the castrate gonadotropic hormone disappear from the urine. This patient was given a total of 50 mg. of stilbestrol in oil, over a period of forty-one days. The urine was negative for castrate gonadotropic hormone during the period of stilbestrol administration and for twenty-one days after the discontinuation of the treatment. The remaining 4 patients were given doses varying from 10 to 26 mg., over periods varying from twelve to forty-seven days, without appreciably affecting the castrate gonadotropic hormone excretion. A detailed report of the effect of stilbestrol upon gonadotropic hormone excretion in the menopause is being made elsewhere.

THERAPEUTIC RESULTS

In this series of 45 patients, improvement was noted in 29; complete relief of symptoms in 8; and no improvement in 8. Improvement, if it did occur, took place within four to five days and maximum relief was achieved at the end of ten days to two weeks. The symptom most easily relieved was the flushes. If other symptoms were present, such as nervousness, weakness, vertigo, etc., they were apparently affected little, if at all. Following the discontinuation of treatment, the symptoms usually recurred within one to two weeks. The rapidity with which symptoms recurred after the discontinuation of the treatment was very striking in all but a few cases.

The sense of well being and increased strength and vigor that are frequently noted following the administration of naturally occurring estrogens were observed infrequently following the use of stilbestrol in this series of cases. In addition to the incomplete therapeutic effects of stilbestrol, toxic symptoms were encountered frequently. In view of the fact that these toxic symptoms seriously detract from the therapeutic value of stilbestrol, they will be presented in some detail.

TOXIC SYMPTOMS

Toxic symptoms were noted in 29 patients (64 per cent). Nausea, vomiting, and vertigo, either singly or in combination, occurred most frequently (25 cases). Three patients complained of pain in the epigastrium and one patient had severe pain in the right upper quadrant, associated with nausea. Two patients had diarrhea in addition to nausea and vomiting. One patient complained of precordial pain, palpitation, and nausea following the ingestion of one tablet of 0.2 mg. of stilbestrol. In some cases toxic symptoms occurred within twenty minutes after oral administration. One patient developed painful edema of the vulva which persisted for two weeks after the discontinuation of therapy. In some patients, toxic symptoms occurred at the beginning of treatment but disappeared as the drug was continued. In contrast to these, some patients did not develop nausea until after the drug had been administered continuously for several days. One patient, who had received intramuscular injections for nine months with complete control of the flushes and without toxic symptoms, developed epigastric pain, nausea, and dizziness at the end of this time. The symptoms subsided within ten days after the stilbestrol was discontinued. The nausea and vomiting usually disappeared within twenty-four hours after discontinuation of the stilbestrol.

tween the morphologic state of the endometrium and the bleeding, since the histologic picture varied from slight proliferation to moderate and advanced proliferation. On the other hand, one patient, following 75 mg. of stilbestrol, showed a hyperplastic endometrium (Fig. 8) without uterine bleeding. There appears to be considerable individual variation in the response of the endometrium to stilbestrol. In one instance, 128 mg. produced slight proliferation, whereas, in another case, 29 mg. were sufficient to produce advanced proliferation.

In one patient, an unusual endometrial pattern was found which will be described here. A preliminary endometrial biopsy on November 25 revealed atrophy (Fig. 5). On November 28 and 29, the patient received 10 mg. of stilbestrol, intramuscularly. Spontaneous uterine bleeding occurred on December 1 and continued for six days. An endometrial biopsy, done on the first day of bleeding, revealed a moderate amount of proliferation (Fig. 6). The stilbestrol was continued in 5 mg. doses daily from December 1 to 6. Another biopsy on December 6 revealed



FIG. 7.

Fig. 7.—Case S. R. Endometrial biopsy following 55 mg. of stilbestrol, showing a mixed picture of proliferative and secretory changes.



FIG. 8.

Fig. 8.—Case C. C. (Aged 48 years; two years postmenopause.) Endometrial biopsy following 75 mg. of stilbestrol, showing advanced proliferation with cystic glands resembling hyperplasia.

an atypical endometrial pattern (Fig. 7). There was a marked increase in the size and number of endometrial glands. Many of the glands were dilated, showed marked vacuolization and pseudostratification. The stroma was edematous and showed increased cellularity. A glycogen stain demonstrated the presence of varying amounts of glycogen. The histologic appearance of this endometrium did not resemble any normal phase or any pattern induced by natural estrogens. The histologic appearance consisted of a combination of marked secretory activity with moderate proliferation. On December 18 and 20, the patient was again given 10 mg. of stilbestrol. On December 26 uterine bleeding recurred and continued for ten days. On January 3 an endometrial biopsy revealed moderate proliferation with no evidence of secretory changes.

part to the patient the feeling of well-being and nervous stability that usually result from treatment with the natural estrogens.

3. Toxic symptoms were observed in 64 per cent of the 45 patients.

4. The toxic symptoms most commonly noted were nausea, vomiting, and vertigo.

5. The high incidence of toxic symptoms, in our opinion, militates seriously against the usefulness of stilbestrol as a therapeutic agent.

REFERENCES

- (1) Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: *Nature*, London 141: 247, 1938. (2) Dodds, E. C., Lawson, W., and Noble, R. L.: *Lancet* 1: 1389, 1938. (3) Palmer, A., and Zuckerman, S.: *Lancet* 1: 923, 1939. (4) Bishop, P. M. F., Boycott, M., and Zuckerman, S.: *Lancet* 1: 5, 1939. (5) Winterton, W. R., and MacGregor, J. N.: *Brit. M. J.* 1: 10, 1939. (6) Geist, S. H., and Salmon, U. J.: *New York J. Med.* 39: 1759, 1939. (7) Varangot, J.: *Bull. Soc. d'obst. et de gynéc.* 28: 160, 1939. (8) Tuscher, H.: *Klin. Wehnschr.* 10: 808, 1939. (9) Karnaky, K. J.: *South. M. J.* 32: 813, 1939. (10) Preissecker, E.: *Zentralbl. f. Gynäk.* 63: 1904, 1939. (11) Salmon, U. J., and Frank, R. T.: *Proc. Soc. Exper. Biol. & Med.* 33: 612, 1936. (12) Frank, R. T., and Salmon, U. J.: *Ibid.* 33: 311, 1935. (13) Albright, F.: *Endocrinology* 20: 24, 1936. (14) Jones, M. S., and MacGregor, J. N.: *Lancet* 2: 974, 1936. (15) (In press.) (16) MacBryde, C. N., Freedman, H., and Loeffel, E.: *J. A. M. A.* 113: 2320, 1939. (17) Shorr, E., Robinson, F. H., and Papanicolaou, G. N.: *J. A. M. A.* 113: 2312, 1939. (18) Buxton, C. L., and Engle, E. T.: *J. A. M. A.* 113: 2318, 1939. (19) Loeser, A. A.: *Brit. M. J.* 1: 13, 1939. (20) Geist, S. H., and Salmon, U. J.: *AM. J. OBST. & GYNEC.* 38: 392, 1939.

A CRITICAL ANALYSIS OF CESAREAN SECTION IN A LARGE MUNICIPAL HOSPITAL*

ABRAHAM B. TAMIS, M.D., F.A.C.S., AND MILTON D. KLEIN, M.D.,
NEW YORK, N. Y.

(From the Obstetrical Service, Morrisania City Hospital)

A PERUSAL of the current literature conveys the impression that the maternal risk of cesarean section is less than 3 per cent.^{1, 3, 8, 11, 12, 15} Occasionally a maternal mortality rate of 5 per cent and 6 per cent is acknowledged.²

The maternal mortality studies of large communities,^{5, 16, 17} which more truly reflect the results for obstetrics as it is generally practiced, yield much higher rates and substantiate the contention of Watson¹ that when all cases are included, the cesarean mortality for the United States is probably from 10 to 15 per cent.

If any advance is to be made in the reduction of cesarean mortality, it is important that every institution should, from time to time, review its records and present the facts for discussion, whether they be good or bad. Before judgment is passed, however, the critic should bear in mind that lower cesarean mortality rates are to be expected where elective sections predominate, and that the mortality percentage

*Read at a meeting of the Section of Obstetrics and Gynecology, The New York Academy of Medicine, February 27, 1940.

Although several theories have been advanced to explain the toxic symptoms (direct irritation of the gastric mucosa, liver damage, direct action on the central nervous system), there is little factual evidence to support them. In an attempt to determine whether the toxic symptoms were attributable to kidney or liver damage, MacBryde, Freedman and Loeffel,¹⁶ Shorr, Robinson and Papanicolaou,¹⁷ and Buxton and Engle,¹⁸ performed liver function tests as well as blood chemistry and urine studies on patients receiving large doses of stilbestrol. None of these workers was able to obtain any evidence indicating liver damage. One of the patients, reported by Buxton and Engle, developed albuminuria during the course of treatment which disappeared after the discontinuation of the stilbestrol. Apparently there were no findings in any of the other cases to indicate impairment of kidney function.

DISCUSSION

It is difficult to explain the marked variation in the incidence of manifestations of toxicity, as reported by different investigators. It is not unlikely that the lack of agreement as to the incidence of toxic effects is not due entirely to variations in dosage or mode of administration but, rather, to personal differences in the evaluation of the symptoms.

It appears that although stilbestrol has estrogen-like properties, as manifested by its proliferative action on the endometrium and vaginal mucosa, it is not a satisfactory therapeutic substitute for the estrogens of the estradiol family. This conclusion is based on the fact that the therapeutic effects of stilbestrol were, in most instances, neither complete nor uniform. Furthermore, it induced toxic symptoms in a large percentage of cases. In this connection, it should be borne in mind that treatment with estrogens is essentially substitution therapy and, for this reason, not infrequently entails the use of the hormone over long periods of time. Moreover, in view of the paucity of information concerning the origin and mechanism of the toxic symptoms induced by stilbestrol, we feel that its use, for the present, should be confined to experimental studies. The synthesis of stilbestrol by Dodds and his co-workers constitutes a brilliant achievement of modern chemistry. It is hoped that further investigations will yield a compound which will preserve the biologic properties of stilbestrol without its distressing clinical by-effects.

SUMMARY AND CONCLUSIONS

1. The biologic and therapeutic properties of stilbestrol were studied in a series of 45 cases. These studies included (a) an evaluation of its effect on the vaginal smear, vaginal mucosa, and endometrium; (b) the capacity of stilbestrol to inhibit the excessive gonadotropic hormone excretion in the menopausal patient; and (c) its effectiveness in relieving the symptoms of the menopause syndrome.

2. These studies have shown that (a) stilbestrol has an estrogen-like effect on the human vaginal mucous membrane and endometrium; (b) if sufficient stilbestrol is administered, it appears to inhibit the excessive gonadotropic hormone in the menopause patient; (c) stilbestrol relieves the hot flushes of the menopause, but it does not im-

tients operated upon for this indication, 6 women died, a maternal mortality rate of 12.7 per cent for the group.

In 11 instances the disproportion was absolute, and elective sections were done immediately on admission with no maternal or fetal deaths.

In the 36 patients with relative disproportion a test of labor was permitted before cesarean section was performed.

Some hospitals have a hard and fast rule that, unless rapid progress is made in six to eight hours, with intact membranes, a cesarean section is to be performed. With this yardstick the patient is operated upon under ideal conditions with a prognosis for recovery not less than 97 per cent. By the same token it is also quite obvious that many women so readily sectioned might conceivably have delivered spontaneously or with the assistance of forceps if given a longer test.

Our practice has been to individualize each case. The test lasted six hours, or even twenty-four hours, depending on the amount of progress made. Vaginal examinations were prohibited. Rectal examinations were done as often as required.

During the past few years our judgment has been somewhat influenced by x-ray pelvimetry. The method used is that described by Weitzner,⁷ which gives a rapid and accurate measurement of the conjugata vera as well as a comprehensive view of the presenting part in its relation to the pelvic inlet.

By following this plan, most of our patients with relative cephalopelvic disproportion were successfully delivered by the vaginal route. In 1938, for example, of 47 full-term primiparas who began labor with an unengaged presenting part, only 2 required a cesarean section. The rest were delivered spontaneously or with forceps, with a loss of only 2 babies and no maternal mortality.

If insufficient progress was made during a test of labor, the baby was delivered by cesarean section (if alive), or by craniotomy (if dead). It is significant and interesting to note that during the period covered by this report craniotomy was resorted to only once.

Of the 36 patients with relative disproportion delivered by cesarean section, 6 died. Four of these deaths were due to peritonitis. The type of cesarean operation chosen was an important factor in causing the high mortality.

Approximately one-half of the 47 patients with cephalopelvic disproportion were operated upon by the classical and the other half by the low segment method (Table II). These operations were performed by the same members of the ob-

TABLE II. CEPHALOPELVIC DISPROPORTION, TYPE OF OPERATION

	CLASSICAL				LOW SEGMENT				PERITONEAL EXCLUSION			
Number of cases	22				24				1			
Primiparas	21				19				1			
Hours in labor	0	0-12	12-24	24+	0	0-12	12-24	24+	0	0-12	12-24	24+
Number of cases	2	9	7	4	-	3	8	13	-	-	-	1
Maternal deaths	-	2*	-	1*	-	1*	1*	1*	-	-	-	-
Hours membranes ruptured	0	0-12	12-24	24+	0	0-12	12-24	24+	0	0-12	12-24	24+
Number of cases	17	5	-	-	6	7	4	7	-	-	-	1
Maternal deaths	3*	-	-	-	-	1*	-	2*	-	-	-	-
Peritonitis	3*				1*				-			
Paralytic ileus	-				1*				-			
Pneumonia	-				1*				-			

*Died.

stetric staff in the same hospital for the same indication, and are therefore comparable for evaluating the superiority of one operation over the other.

Those treated by the classical cesarean section had the advantage of intact membranes and shorter duration of labor. In spite of this, 3 patients (13.6 per

is likely to rise when emergency and other nonelective sections constitute the greater proportion of cases.

This report is based on a review of all cesarean operations at Morrisania City Hospital, one of several municipal hospitals in the City of New York. The Obstetrical Service was organized in October, 1929. Up to Dec. 31, 1937 there were 14,489 deliveries. More than one-half of the obstetric admissions are referred from the Out-patient Antepartum Clinic. The remainder either apply directly or are transferred from other municipal hospitals. About 20 to 30 per cent of the in-patients are colored. The service is supervised by the attending staff, resident, and assistant resident.

STATISTICAL RÉSUMÉ

One hundred and twelve cesarean sections were performed, an incidence of 0.8 per cent, or 1 section in 129 deliveries. The average cesarean incidence in New York City is two to four times higher, or about 1 section in 25 to 50 deliveries. It would appear from this that we have either been very conservative in the management of the various obstetric difficulties for which cesarean section might be indicated, or that we have been rather fortunate in having a minimum of patients requiring this procedure. We believe that the explanation of our low incidence is due to a conservative policy. In fact from a consideration of the data which follow, we may have carried this policy too far in some instances.

Our uncorrected maternal mortality rate for cesarean section is 10.7 per cent. However, this high death rate is not reflected in our uncorrected general maternal mortality rate for the same period, which is 5.3 per thousand living births. This result compares favorably with that of other similar institutions.

The indications for which cesarean sections were done at our institution are enumerated in Table I.

TABLE I. INDICATIONS FOR CESAREAN SECTION

		NUMBER CASES	MATERNAL DEATHS
Cephalopelvic disproportion		47	6
Contracted inlet	42		
Contracted outlet	2		
Normal pelvis	3		
Previous cesarean section		19	1
Placenta previa		19	2
Central	15		
Partial	4		
Premature separation of placenta		10	2
Complete	9		
Partial	1		
Obstructing tumor		6	-
Cardiac disease		4	-
Eclampsia		1	1
Rupture of uterus		2*	-
Previous attempt at delivery		1	-
Vaginal stenosis		1	-
Cervical stenosis		3	-
Total		112	12

*One case included in group of "previous cesarean section."

Cephalopelvic Disproportion.—This constituted the largest of the groups (41 per cent). The problem for the obstetrician is identical whether the baby is too large for the pelvis or the pelvis too small for the baby. Of the 47 pa-

TABLE IV. PLACENTA PREVIA, TYPE OF OPERATION

	CLASSICAL			LOW SEGMENT			PERITONEAL EXCLUSION		
Number of cases	12			6			1		
Multiparas	6			6			1		
Months' gestation	7	8	9	7	8	9	7	8	9
Number of cases	1	6	5	-	2	4	-	1	-
Stillbirth	-	1	-	-	-	-	-	-	-
Neonatal death	1	3	-	-	1	-	-	-	-
Maternal death	-	-	2	-	-	-	-	-	-
Blood transfusion	3			4			-		
Peritonitis	1*			-			-		
Embolism	1*			-			-		

*Died.

Cesarean section has been used mainly in the interest of the mother. We have adhered strictly to the principle of delivering all patients with central placenta previa by cesarean section no matter what the period of gestation.

The method of delivery in patients with partial placenta previa has been left to the discretion of the staff. Thus only 4 such patients were treated by cesarean section.

The recent literature indicates that many obstetricians are extending the use of cesarean section to include most cases of partial placenta previa and some of the marginal placenta previas.¹²⁻¹⁵ It is conceivable that on further study of our statistics on placenta previa partialis, our indications for section may be broadened to include an increasing number of these cases.

The low segment operation was done in 6 instances and found to be as applicable for the treatment of this complication as the classical cesarean section except that more bleeding was encountered when the placenta was located under the line of incision.

Premature Separation of the Placenta.—Until recently all cases of the complete variety (ablatio placentae) have been treated by cesarean section. The milder or partial placental separations were all delivered vaginally.

Of the 10 patients sectioned, 2 died; 1 of peritonitis and the other of toxemia (Table V). Both were in poor condition at the time of operation notwithstanding previous transfusions. The maternal mortality for this group was 20 per cent.

TABLE V. PREMATURE SEPARATION PLACENTA, TYPE OF OPERATION

	CLASSICAL	LOW SEGMENT
Number of cases	8	2
Maternal deaths	2	-
Stillbirth	6	1
Neonatal death	1	1
Peritonitis	1*	-
Toxemia	1*	-

*Died.

The superior results claimed by the advocates of the Dublin routine for the treatment of complete separation of the placenta have impressed us considerably. The technique consists of rupturing the membranes, packing cervix and vagina, repeated injections of pituitrin, application of a Spanish windlass, replacement of blood loss by large transfusions, and prompt delivery when full dilatation is obtained. We applied this routine in the last 3 cases of ablatio placentae seen on the wards. Our courage faltered after observing the first case for twelve hours as the patient seemed to be going downhill. She was delivered by a classical cesarean section. When the next 2 patients were admitted we determined to carry out the method to completion, and did. Both patients made an uneventful recovery.

cent) died of peritonitis. Of the low segment group, only 1 patient (4 per cent) died of the same cause. The security against peritoneal infection for the low segment operation was three times greater than that for the classical cesarean section.

Previous Cesarean Section.—Of the total number of patients admitted to the hospital with a history of a previous section, 19 women required a repeated operation. Eighteen were registered in our Prenatal Clinic and were instructed to enter the hospital at the first sign of labor. Thus it happens that most of the patients were admitted under ideal conditions, with membranes intact and in labor less than six hours (Table III). One patient died, a mortality of 5.2 per cent for this group.

TABLE III. PREVIOUS CESAREAN SECTION, TYPE OF OPERATION

	CLASSICAL			TWO FLAP			PORRO		
	0	0-12	12-24	0	0-12	12-24	0	0-12	12-24
Hours in labor	10	6	-	-	1	1	-	1*	-
Maternal deaths	1	-	-	-	-	-	-	-	-
Hours membranes ruptured	Int.	0-6	6-12	Int.	0-6	6-12	Int.	0-6	6-12
	14	1	1	2	-	-	1	-	-
Maternal deaths	1	-	-	-	-	-	-	-	-
Stillbirths	0			0			1		
Neonatal deaths	0			0			0		
Peritonitis	1 (died)			0			0		

*Ruptured uterus.

Our attitude toward patients who have been previously sectioned is more elastic than is permitted by the adage "once a cesarean, always a cesarean." If the previous section was performed for indications other than obstructed labor, and if the post-partum course was not complicated by morbidity, the patient was allowed a test of labor, *provided she remained under observation from the very onset*. If rapid and progressive advancement appeared within a relatively short time, delivery was allowed to be completed normally or assisted with forceps. If labor slowed up for any cause, a cesarean section was done.

For example, during the year 1934 alone, 7 patients were admitted with a history of having had a previous section. Three patients delivered spontaneously and one was assisted by forceps. The remaining three patients were subjected to section immediately on admission because of a contracted pelvis.⁶

One patient, a negress, disobeyed instructions and remained at home while in labor with the hope of delivering spontaneously. A few hours later the uterine scar gave way and she was brought to the hospital in shock due to a ruptured uterus and an intra-abdominal hemorrhage. A Porro section was done. The fetus was stillborn. The patient had a stormy convalescence but fortunately recovered.

The patient who died had a large incisional hernia which was repaired immediately after the section was completed. Autopsy examination indicated an extension of a *Staphylococcus aureus* infection of the abdominal wound into the general peritoneal cavity. The uterine incision was uninvolved. This death was preventable. It taught us to restrict our surgery during cesarean section to actual necessities, and postpone to some later date other procedures which increase the risk to the patient.

Placenta Previa.—(Table IV.) Nineteen patients with placenta previa were treated by cesarean section. Of these, 15 were central and 4 were partial. Two mothers died, one of embolism and one of peritonitis. The maternal mortality for this group was 10.5 per cent. The patient who died of peritonitis had a classical section within three hours of the initial hemorrhage and immediately after only one vaginal examination.

Six infants died. All were premature. Only 3 could be considered viable.

Unsuccessful Attempt at Delivery.—The danger of performing a cesarean section, after previous attempts at delivery have been unsuccessful, is appreciable. Kerr⁴ quotes maternal mortality rates under such conditions as high as 15 to 20 per cent. He advocates craniotomy as the method of choice, because the fetus is dead as a rule, and the risk is less unless the pelvis is markedly contracted.

Our experience at Morrisania City Hospital with this type of patient has been limited to 2 patients, both of whom were admitted in shock. One was treated by craniotomy. The other was subjected to a Hirst peritoneal exclusion operation because of extensive bladder injury which followed an attempted version in another hospital. The trauma to the bladder precluded any possibility of doing a Latzko or a low segment operation. Both these patients recovered after a stormy convalescence.

Stenosis of the Vagina and of the Cervix.—A douche of undiluted lysol in an attempt to produce an abortion resulted in an extensive cicatrization of the vagina in one case which made cesarean section mandatory.

Three patients with cervical stenosis due to a previous trachelectomy were delivered by vaginal section in one instance and by abdominal section in two.

There were no maternal or fetal deaths in this group.

Maternal Mortality.—The cause of our maternal deaths following cesarean section are listed in Table VII. Peritonitis took the heaviest toll, accounting for

TABLE VII. CAUSES OF DEATH

	TOTAL CASES	INDICATION FOR OPERATION					TYPE OPERATION	
		PREV. SECT.	CONT. PELVIS	PLAC. PREV.	PRE. SEP. PLACENTA	ECLAMPSIA	CLASSICAL 70 CASES	LOW SEGMENT 37 CASES
Peritonitis	7	1	4	1	1	-	6 (8.5%)	1 (2.7%)
Pulmonary embolus	1	-	-	1	-	-	1	-
Paralytic ileus	1	-	1	-	-	-	-	1
Bronchopneumonia	1	-	1	-	-	-	-	1
Toxemia	2	-	-	-	1	1	2	-

7 (58.3 per cent) of the 12 deaths. At least two of these deaths may be considered as preventable, because autopsy revealed the infection to have been introduced at the time of operation.

The two patients who died of toxemia were critically ill at the time of admission and died in less than twenty-four hours. The eclamptic patient was not a suitable risk for abdominal surgery. The operation was used as a measure of last resort since death appeared inevitable.

DISCUSSION

The prevention of peritonitis deserves intensive investigation as it causes from 40 to 50 per cent of deaths following cesarean section.^{5, 8, 15}

The relation of ruptured membranes, duration of labor, and vaginal examination to the spread of infection during labor requires no discussion. Their importance has been adequately stressed by previous studies and needs no further emphasis here.

Two other factors, however, have played a prominent role in our incidence of peritonitis, namely: introduction of infection at the operating table; and type of operation selected.

The incidence of our wound infections, which fortunately consisted mostly of mild stitch abscesses, was close to 20 per cent in spite of the

It was a trying experience, for it meant constant surveillance and concerted cooperation on the part of the nursing and interne staffs. We feel that the Dublin method should be used only where blood transfusions can be readily obtained and where a trained personnel is always available. Lacking such facilities, the interest of the patient is best served by a cesarean section.

Obstructing Tumors (Table VI).—This group is mainly of interest because of the variety of pelvic masses found obstructing vaginal delivery. There were 2 cases of cervical fibromyomas, and one each of embryonal tumor of the ovary, dermoid cyst of the ovary, pelvic kidney, and retroperitoneal sarcoma.

TABLE VI. OBSTRUCTING PELVIC TUMORS

Cervical fibromyoma	2 cases
Embryonal tumor of ovary	1 case
Dermoid cyst of ovary	1 case
Pelvic kidney	1 case
Retroperitoneal sarcoma	1 case

There were no maternal deaths. The one neonatal death resulted from prematurity.

Cardiac Disease.—Cesarean section as means of terminating labor in patients with heart disease was resorted to in four instances. One case was a primiparous cardiac who had been hospitalized for twenty-four days because of decompensation. The other three were multiparas with histories of previous decompensations in whom sterilization was advocated and a cesarean section done, therefore, at term to effect this procedure.

All these patients were functionally classified as Class 2b. In spite of a poor myocardium they were able to withstand the strain of the operation. One patient eviscerated on the twenty-first day postoperative, then developed a bronchopneumonia and pleural effusion, but survived. The case illustrates the difficulty of judging the cardiac reserve until the heart is actually under stress.

The classical section was employed in each instance because of the rapidity with which it can be performed and because of the access to the Fallopian tubes. There were no maternal or fetal deaths in this small group.

A point worth emphasizing is the choice of anesthesia and the manner of its administration. Patients with heart disease are very prone to develop pulmonary complications. For this reason the anesthesia should be given by an expert anesthetist. We prefer the use of gas-oxygen inhalation.

Eclampsia.—We have not found it necessary to resort to cesarean section for pre-eclampsia. Our experience with a modified Stroganoff regime followed by induction of labor has proved most satisfactory.

Perhaps the same conservative attitude may also be taken with the convulsive states. We had an unfortunate experience with the only patient with eclampsia who was treated surgically. This woman, a nonclinic primipara, was admitted to the hospital in coma, with frequent convulsions and was practically moribund. Examination revealed her to be at term and not in labor. A classical cesarean section was done under ethylene anesthesia but the patient died twenty-four hours later.

Rupture of the Uterus.—Included in this series are two cases of rupture of the uterus. One occurred through a previous cesarean scar. The other had a spontaneous rupture of the uterus. This patient, a thirty-six-year-old multipara, was admitted to the hospital in shock after having had abdominal pains for eight hours. The cervix was 1 finger dilated, membranes were intact, presenting part unengaged, and there was no external evidence of bleeding. She was given a transfusion but failed to rally. The diagnosis of rupture of the uterus was then suspected and a laparotomy performed. Free blood was present in the peritoneal cavity and found to originate from a tear in the anterior wall of the uterus. A stillborn baby was delivered through this tear and the uterus closed in layers. Convalescence was uneventful.

10.7 per cent. The general uncorrected maternal mortality rate for all deliveries, spontaneous and operative, is 5.3 per thousand living births.

2. The indications for cesarean section are separately considered and the errors in judgment and technique discussed.

3. The superiority of the low segment operation over the classical section is confirmed.

4. The role of peritonitis as a cause of maternal mortality following this operation is stressed. The probable causes for this complication at Morrisania City Hospital are enumerated and the methods described whereby its occurrence may be reduced.

The authors wish to acknowledge the assistance of Dr. Milton J. Goodfriend in organizing the material for this paper.

REFERENCES

- (1) *Watson, Benj. P.*: Surg. Clin. North America 17: 1, 1937. (2) *Reddoch, Jos. W., and Howell, R. P.*: New Orleans M. & S. J. 89: 625, 1937. (3) *Campbell, J. V.*: AM. J. OBST. & GYNEC. 33: 451, 1937. (4) *Kerr, J. M. Munro*: Operative Obstetrics, ed. 4, Baltimore, 1937, William Wood & Co. (5) New York Academy of Medicine, Committee on Public Health Relations: Maternal Mortality in New York City. A Study of All Puerperal Deaths, 1930-1932, Commonwealth Fund, 1933. (6) *Tamis, Abraham B., and Clahr, Jacob*: J. A. M. A. 109: 195, 1937. (7) *Weitzner, S. F.*: AM. J. OBST. & GYNEC. 30: 126, 1935. (8) *Soule, S. D.*: Ibid. 36: 648, 1938. (9) *Waters, Edward G.*: AM. J. OBST. & GYNEC. 39: 423, 1940. (10) *Harris, L. J.*: Canad. M. A. J. 37: 32, 1937. (11) *Schumann, Edward A.*: AM. J. OBST. & GYNEC. 37: 212, 1939. (12) *Daily, Edwin F.*: Surg. Gynec. Obst. 59: 106, 1934. (13) *Phaneuf, Louis E.*: New York J. M. 34: 641, 1934. (14) *Siegel, Isidore A.*: AM. J. OBST. & GYNEC. 27: 889, 1934. (15) *Daichman, Isidore, and Pomerance, William*: Ibid. 37: 137, 1939. (16) Maternal Mortality in 15 States, U. S. Dept. of Labor, Children's Bureau, Publication No. 223, Washington, D. C., 1934. (17) Maternal Mortality in Philadelphia, 1931-1933, Philadelphia County Medical Society, Philadelphia, 1933.

MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS*

IRA C. SKINNER, M.D., AND JOHN R. McDONALD, M.D.,
ROCHESTER, MINN.

(From the Mayo Clinic)

MALIGNANT neoplasms are occasionally found in which there is differentiation into a type of cell entirely foreign to the organ in which it is primary. Some of these neoplasms can be explained as arising in teratomas while in others no such explanation is possible. Primary osteogenic sarcomas have been described in the thyroid gland (Broders and Pemberton¹) and in the breast. Squamous cell carcinomas are of frequent occurrence in the bronchus and yet squamous epithelium is not normally found here. Squamous epithelium has been described in the gall bladder (Broders²), prostate (Burrows and Kennaway³), ducts of the pancreas, and gastrointestinal tract (Vinson and Broders⁴).

*Abridgment of thesis submitted by Dr. Skinner to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in surgery.

Submitted for publication April 26, 1940.

most rigorous precautions in preparing the abdomen for operation. Autopsies on two of the seven deaths from peritonitis clearly indicated an extension of the infection from the abdominal wound to the general peritoneal cavity.

In checking over the possible sources for this break in technique, the operating room itself came under suspicion. The hospital has two major operating rooms for the use of all surgical cases. As less than 50 per cent of our cesarean sections were elective, not infrequently the operation followed shortly after a potentially or actually infected surgical case. The nursing personnel remained the same for both operations. It is not difficult, therefore, to imagine cross-infection under such circumstances.

We believe, with DeLee and others, that the obvious remedy is a complete operating room unit for the exclusive use of cesarean section, with nursing personnel devoted only to this division. Arrangements to incorporate such a unit on our obstetric floor have already been made.

The second factor of importance affecting the incidence of peritonitis is related to the type of cesarean operation selected. The classical cesarean section was performed on 70 patients. Six died of peritonitis, a maternal death rate of 8.5 per cent. The low segment operation was performed 37 times with one death from peritonitis, a maternal death rate of 2.7 per cent.

As was described under "cephalopelvic disproportion," the conditions under which the low segment operation was performed were less favorable than those of the classical group. Nevertheless, notwithstanding this disadvantage, the low segment operation gave three times more security against the occurrence of peritonitis.

The classical cesarean section should be utilized only where speed is necessary or where it is essential to perform other operative procedures. It is safer for the patient, however, to resort to the low segment operation, the Latzko extraperitoneal operation, or the approach to the lower uterine segment recently described by Waters.⁹

The final criterion of obstetric management does not rest on the end results of any one operative procedure but on the outcome of all deliveries, normal or otherwise. This information may be obtained from general maternal mortality rates which are uncorrected. In New York City, this rate is said to be 6.1 per thousand living births.⁵ In the very best hands in English hospitals, the rate is 5.8.¹⁰ At Morrisania City Hospital, the rate is 5.3, notwithstanding a relatively high maternal mortality for cesarean operations. Therefore, we feel justified in maintaining our present policy toward the obstetric patient, except for the few changes already mentioned.

SUMMARY AND CONCLUSIONS

1. An analysis of cesarean sections at Morrisania City Hospital is presented. The incidence of this operation is 0.8 per cent, or one in 129 deliveries. The uncorrected cesarean maternal mortality rate is

mucus. Here, it dips down into complicated racemose glands. In the cavity of the uterus the epithelium becomes ciliated, low, and cylindrical; it forms into simple tubular glands that secrete a thin albuminous substance. In the tubes the epithelium is more richly ciliated, low, and nonglandular and covers the delicate rugae that line the tubal lumina. Since the entire system is formed from a common progenitor, the advocates of this hypothesis hold that these undifferentiated cells may remain in adult life and later might produce a squamous type of epithelium.

Such a hypothesis requires the identification of such cellular rests in the endocervix and uterine fundus. Meyer¹² found certain small cells beneath the cylindrical epithelium of the cervix, which he interpreted as representing the rests of basal cells from squamous epithelium that previously covered that region of the cervix. Krompecher¹⁴ maintained that the cylindrical epithelium had an undifferentiated basal layer capable of forming epithelium. Schmidt¹⁵ in studying regeneration of cylindrical cells in the cervix attached considerable importance to certain round cells which he found in profusion in rapidly growing polyps and in erosion. He expressed the opinion that these cells played an important role in regeneration and were not wandering cells or leucocytes.

A direct implantation of squamous epithelium by contact has been suggested by some, as an explanation for the occurrence of squamous epithelium at the tip of a glandular endocervical polyp. Reis¹⁰ spoke of a "sort of infection with pavement epithelium brought about by contact with organs covered with the same variety of epithelium."

Another explanation that has been suggested is that the squamous and glandular tumor cells have arisen from different epithelium, the two tumors developing simultaneously and becoming intimately mixed ("doppel tumor" or "collision tumor"). Kaufmann¹⁶ reported a case of mixed cell carcinoma of the uterine body which he concluded arose from the simultaneous malignant proliferation of the thickened metaplastic surface epithelium and of the glandular epithelium.

A genuine metaplasia of epithelium has been offered as the explanation for the changes in the cervix and uterine body. Kettle¹⁷ has called attention to the polymorphism of the malignant epithelial cell and Herxheimer¹⁸ as early as 1907 expressed the opinion that in mixed squamous cell carcinoma and adenocarcinoma, a single parenchyma was present, developed from an undifferentiated embryonic foundation capable of differentiation in two directions. It has been implied by some investigators that the squamous epithelial cell originates directly from the columnar cell. However, Broders^{2, 4} has felt that the columnar cell is differentiated and cannot produce a squamous epithelial cell, but rather that the regenerative cell has the inherent capacity of producing either a glandular or secretory type of cell or a squamous or protective type of cell. Murray¹⁹ has offered adequate experimental proof that the power to differentiate either into squamous cells or glandular cells resides in the regenerative cell. He succeeded in producing squamous cell carcinoma and adenocarcinoma by transplants of a mixed cell tumor from the left axilla of a mouse.

METHOD OF STUDY

All mixed adenocarcinoma and squamous cell carcinoma of the uterus seen at the Mayo Clinic from Jan. 1, 1915, to May 31, 1938, inclusive, constituted the material for study. Several blocks of tissue were taken from various portions of the tumor in those cases in which hysterectomy had been performed. Permanent sections were then made by the frozen section technique and stained with hematoxylin and eosin. In a few cases, especially where there was doubt as to the presence of glandular elements in the carcinoma, a mucous stain was done. Biopsy material alone was available in some of the cases. In these, the original mounted microscopic sections were used.

In cases in which hysterectomy had been performed, the extent of the growth in the uterus was determined by frozen sections stained with

Squamous cell carcinomas have been demonstrated to occur in all of these locations. Occasionally a carcinoma develops in an organ containing glandular epithelium in which a portion of the tumor retains the glandular character of the epithelium from which it arises while the cells in another part differentiate into pearly bodies and assume the characteristics of malignant squamous epithelial cells. For this type of neoplasm the terms "adenocarcinoid" and "adenocanthoma" have been coined.

REVIEW OF LITERATURE

The replacement of columnar epithelium by benign squamous epithelium in the uterus has been given various names, including ichthyosis uteri, psoriasis uteri, epidermization, squamous metaplasia, leucoplakia, epidermalization, and epidermoidization. Gautier,⁵ at the International Medical Convention at Geneva, was the first to describe a case in which the uterine cavity was lined by stratified squamous epithelium very similar to the epithelium of the skin and vagina. Zeller⁶ in 1885 fully discussed this condition. At this time it was customary to treat various uterine disorders by intrauterine applications of caustics such as iodine and formaldehyde. In those patients treated intensively, the entire uterine mucosa became firm and epidermal in character. Fifty per cent of his patients in whom the endometrium had been replaced by squamous epithelium had received such treatment. He expressed the opinion that chronic irritation played an important role in initiating the change from columnar to squamous epithelium in the endometrium.

Mainzer⁷ also noted squamous epithelium in the uterine cavity following formalin vaporizations. Squamous epithelium has been found in gonorrheal endometritis (Wertheim and Menges⁸), in endometrial tuberculosis (von Franque⁹), and in pyometra. It is common knowledge that the endometrium of the everted uterus may be replaced by squamous epithelium (Ries¹⁰). Fluhmann¹¹ described epidermalization in the cervix and in cervical polyps. In his entire series of 59 cases in which this occurred in the cervix, there were definite signs of chronic irritation. Therefore, he stated that the phenomenon occurred in the adult as the result of chronic irritation in the form of an inflammatory reaction. Various hypotheses have been offered to explain this replacement of columnar by squamous epithelium in the uterus.

It has been suggested that the squamous epithelium may be an ingrowth from the basal layer of normal adjacent squamous epithelium, the extension taking place along the trellis furnished by the gland framework. However, this would not explain the occurrence of squamous epithelium at the tip of a glandular mucous polyp of the endocervix in which there is an isolated nest of squamous epithelial cells at the tip, but where the rest of the polyp including the base is covered by columnar epithelium. Neither does this explain the presence of squamous cell carcinoma in the uterine fundus in which there is no connection with the squamous epithelium of the cervix.

Meyer¹² has shown that, during the third or fourth month of intrauterine life, the squamous epithelium extends high into the cervical canal. At the sixth month, columnar epithelium grows down replacing this and gives the histologic picture usually seen in the adult cervix. Meyer postulated that in this transition basal cells are left beneath the glandular epithelium. At a later date, there is a weakening of the cylindrical cell lining and the rests of basal cells begin to proliferate, producing a squamous epithelial lining.

Another explanation for the presence of squamous epithelium in these locations is that they originate in cellular rests. The genital tract is formed by the fusion of the Müllerian cords (Graves¹³). Thus, the membrane lining the entire canal has a common origin and constitutes the so-called "Müllerian epithelium." The Müllerian epithelium is not uniform in its final development but takes on specific modifications in each of the organs of the genital tract to meet different functional requirements. In the vagina and vaginal portion of the cervix it assumes an epidermal form much like that of the skin, while in the endocervix, the epithelium becomes high and columnar similar to that of the intestines and secretes a true

of routine carcinoma of the cervix found that more than 50 per cent of their cases occurred after the menopause while in 20 per cent of the cases the disease occurred before the age of the menopause; thus less than 30 per cent occurred during the menopause. In the mixed adenocarcinoma and squamous cell carcinoma of the body of the uterus, 9, or 82 per cent, occurred after the menopause. This establishes mixed tumors of the uterine body as a postmenopausal disease.

SYMPTOMS AND SIGNS

One of the so-called cardinal triad of symptoms (Miller²⁸), namely, bleeding, leucorrhea, and pain, was offered as their chief complaint (Table II) by practically all of the patients in this group. These symptoms do not differ from those found in routine carcinomas of the uterus.

TABLE II. CHIEF COMPLAINTS OFFERED BY PATIENTS WITH MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS

CHIEF COMPLAINT	CERVICAL CARCINOMA		UTERINE CARCINOMA	
	NO.	PER CENT	NO.	PER CENT
Abnormal vaginal bleeding	8	48	6	55
Leucorrhea	4	23	2	18
Abdominal pain	4	23	3	27
Others	1	6	0	0
Total	17	100	11	100

On examination of these patients, it was found that in 64 per cent with mixed squamous cell carcinoma and adenocarcinoma of the cervix the carcinoma had infiltrated the parametrial tissue, whereas in those of the fundus only one had obvious metastasis although two others were considered inoperable because of extension of the growth.

TREATMENT

Radium was applied to the cervix in all 17 cases in which the cervix was the site of the carcinoma. In 5 instances it was used as an adjunct to total abdominal hysterectomy; in 11 instances it was supplemented by roentgen therapy. Three of the 5 hysterectomies were of the Wertheim type. In 9 patients in whom the lesion was located in the uterine fundus, hysterectomy was done. Seven of these were abdominal hysterectomies, and 2 were performed by the vaginal route. In 7 cases the hysterectomy was supplemented by roentgen therapy. In 3 cases radium alone was used because of the inoperability of the lesion.

COMPLICATIONS TO TREATMENT

In one patient receiving limited irradiation for carcinoma of the cervix, pelvic peritonitis and pneumonia developed. Uremia occurred in 2 patients in whom the Wertheim type of hysterectomy was carried out for carcinoma of the cervix. Rather severe cystitis developed in one patient receiving a complete course of irradiation for carcinoma of the body of the uterus.

RESULTS

Of the patients with mixed adenocarcinoma and squamous cell carcinoma of the cervix, 13 were treated five years or more ago, while 7 of the 11 patients with mixed cell carcinomas of the uterine body were treated during this period. Twenty-three per cent of the patients with carcinomas of the cervix who could be traced and 85 per cent with carcinomas of the fundus survived five years or more. Bowling and Fricke,²⁹ in reviewing 1,491 cases of carcinoma of the cervix, had a five-year survival rate of 26.8 per cent. Stacy,³⁰ in 215 cases of carcinoma of the body of the uterus of all grades, found that 59.53 per cent were living five years or more following operation.

Terry's polychrome methylene blue. The case histories were then carefully analyzed so that the clinical course in these patients could be compared with the course in pure squamous cell carcinomas of the cervix and in pure adenocarcinomas of the body of the uterus.

INCIDENCE

Mixed adenocarcinoma and squamous cell carcinoma of the uterus is a relatively rare tumor. Only 28 proved cases have been seen at the Mayo Clinic in twenty-five years. Eleven of these occurred in the body of the uterus and 17 in the cervix. They constituted approximately 1 per cent of the total number of uterine carcinomas seen during this period.

AGE

The age incidence of patients with this type of tumor is shown in Table I. As is apparent the greatest number of cases fall in the same age groups as do the ordinary cellular types of carcinoma of the uterus (Bowling and Fricke,²⁰ Norris and Dunne,²¹ Healy,²² Goldstine²³); 70.6 per cent of mixed cell carcinomas of the cervix and 72.8 per cent of mixed carcinomas of the uterine body occur between the ages of forty and sixty years. The mixed cell tumors of the uterine body occurred in a slightly older age group than those in the cervix, as might be expected (Davis,²⁴ Donald and Shaw,²⁵ Healy and Cutler,²⁶ and Kelly²⁷), the average ages being, respectively, fifty-five and fifty-one years. This corresponds closely to the usual age of occurrence of squamous epithelioma of the cervix and adenocarcinoma of the body of the uterus. The youngest patient in the series was 29 years old and the oldest 70 years; in both of these the neoplasm was located in the cervix.

TABLE I. AGE INCIDENCE OF MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF UTERUS

AGE, YEARS	TOTAL		CERVIX		BODY	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
20-29	1	3.6	1	5.9	0	0
30-39	0	0	0	0	0	0
40-49	11	39.3	7	41.2	4	36.4
50-59	9	32.1	5	29.4	4	36.4
60-69	6	21.4	3	17.6	3	27.2
70+	1	3.6	1	5.9	0	0
Total	28	100.0	17	100.0	11	100.0
Average age	53 years		51 years		55 years	

In review of the literature, one is led to believe from reports of isolated cases that the so-called adenoacanthoma of the uterine body occurs much later in life than does the ordinary adenocarcinoma of the body of the uterus. This has led many to subscribe to the hypothesis that the mixed type of neoplasm originates in an area of senile leucoplakia in which the glandular epithelium is replaced by squamous epithelium. However, in this series there seems to be little difference between the age of occurrence of the mixed adenocarcinoma and squamous cell carcinoma and that of the usual adenocarcinoma of the corpus uteri.

In this group there was only a slight difference in the number of full-term deliveries in cases of malignant lesions of the cervix and the body of the uterus. The average number of deliveries was 1.0 in these individuals in whom mixed cell carcinoma of the uterus subsequently developed, and 2.5 in those in whom mixed cell carcinoma of the cervix subsequently developed.

It is interesting to note that six patients (35 per cent) with mixed adenocarcinoma and squamous cell carcinoma of the cervix had symptoms suggesting the menopause at the time of the original examination, while 10 (59 per cent) were in the postmenopausal state. Bowling and Fricke²⁰ in an analysis of 214 cases

COMMENT

It can be seen that the symptoms, rapidity of growth as measured by the grade of malignancy, and prognosis of mixed squamous cell carcinoma and adenocarcinoma of the uterine cervix do not differ appreciably from those of ordinary squamous cell carcinoma in the same location. Similarly mixed adenocarcinoma and squamous cell carcinoma of the uterine fundus does not differ materially from adenocarcinoma of the fundus.

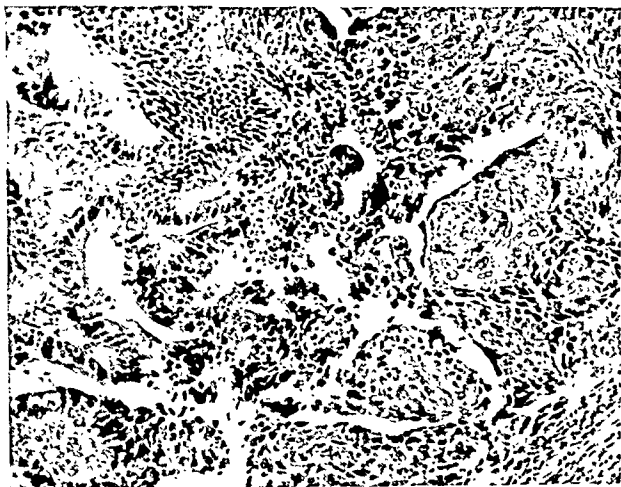


Fig. 1.—Mixed squamous cell carcinoma and adenocarcinoma of the cervix. The squamous cell carcinoma is differentiating into pearls (hematoxylin and eosin $\times 170$).



Fig. 2.



Fig. 3.

Fig. 2.—Mixed adenocarcinoma and squamous cell carcinoma of the cervix. There is a small island of squamous cell carcinoma (hematoxylin and eosin $\times 95$).

Fig. 3.—Mixed adenocarcinoma and squamous cell carcinoma of the uterine body (hematoxylin and eosin $\times 70$).

PATHOLOGY

Grade.—All of these tumors were graded on a basis of 1 to 4 according to the classification laid down by Broders.^{2, 31-33} As may be seen from Table III, 83 per cent of the carcinomas of the cervix were Graded 3 or 4 and 11 per cent were Graded 1 or 2, whereas 82 per cent of the carcinomas of the body of the uterus were Graded 1 or 2. These percentages are in fairly close agreement with those usually given for ordinary carcinomas of the cervix (Bowing²⁹) and of the body of the uterus. In only two cases was there a mixture of grades in the same tumor. One of these occurred in the cervix proper and the other in the uterine body. Both of these tumors were Graded 3 as to the squamous cell carcinoma and 2 as to the adenocarcinoma.

TABLE III. GRADES OF MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS

GRADE	CERVIX		BODY	
	NO.	PER CENT	NO.	PER CENT
1	0	0	1	9
2	2	11	8	73
3	10	59	1*	9
4	4	24	0	0
2 grades	1†	6	1‡	9
Total	17	100	11	100

*Mixed adenocarcinoma and squamous cell carcinoma Grade 3 at internal os and Grade 1 adenocarcinoma in left horn of the uterus.

†Grade 2 adenocarcinoma and Grade 3 squamous cell carcinoma of the cervix.

‡Grade 2 adenocarcinoma and Grade 3 squamous cell carcinoma of the uterine body.

One case is of particular interest in that the uterus contained two separate carcinomas, a Grade 1 adenocarcinoma in the left horn of the uterus and a Grade 3 mixed squamous cell carcinoma and adenocarcinoma at the internal os. This case has previously been reported by Counseller and Butsch.³⁴

Location and Extent of the Carcinoma.—In the 14 cases in which the uterus was available, an attempt was made to determine the extent of the lesion in the uterus by numerous blocks of tissue taken from the margin of the tumor and cut by the frozen section technique. Of the 14 specimens studied, the primary carcinoma was considered endocervical in 5 cases and fundal in 9 cases. In the entire series there were only 2 cases in which there was doubt as to whether the carcinoma should be considered as cervical with invasion of the body of the uterus or fundal with invasion of the cervix. In these cases the opinion of the pathologist who saw the fresh specimens was taken. One of the doubtful cases was considered by the pathologist as originating in the cervix and the other in the body of the uterus.

The cervical carcinomas varied in size from a lesion measuring 1 cm. by 1 cm. by 1 mm. to one involving the entire cervix and body of the uterus. The smallest carcinoma of fundal origin measured 3 by 3 by 2 cm; the largest involved the entire endometrium.

Relative Amounts of Squamous and Adenomatous Element in the Tumor.—A review of the several slides on each specimen was undertaken to estimate whether the adenomatous or squamous element was in the majority throughout the tumor. In the cervical carcinomas, the adenomatous or squamous elements predominated in approximately an equal number of cases (Figs. 1 and 2), the squamous element being in the majority in 9 tumors and the glandular in 8 tumors. On the other hand in the entire 11 cases of carcinoma of the body of the uterus, the adenomatous element was predominant (Fig. 3).

Associated Neoplasms.—Leiomyomas of the uterus were frequently associated with the carcinomas in this series. In 4 of the 5 cases in which hysterectomy had been performed for carcinoma of the cervix, leiomyomas were demonstrated in the uterine musculature. In one other case supravaginal hysterectomy had been performed six years previous to the occurrence of the carcinoma of the cervix because of leiomyoma. In 5 of the 9 patients who had had hysterectomy for carcinoma of the body of the uterus, leiomyomas were also present.

of the cervix were Graded 3 and 4, according to Broders' classification, whereas 82 per cent of the carcinomas of the uterine body were Graded 1 and 2. In mixed cell carcinomas of the cervix neither glandular nor squamous cell elements predominated, whereas the adenomatous element was predominant in all cases of carcinoma of the body of the uterus.

REFERENCES

- (1) *Broders, A. C., and Pemberton, J. deJ.*: Surg. Gynec. Obst. 58: 100, 1934.
- (2) *Broders, A. C.*: Minnesota Med. 8: 726, 1925. (3) *Burrows, Harold, and Kennaway, N. W.*: Am. J. Cancer 20: 48, 1934. (4) *Vinson, P. P., and Broders, A. C.*: J. Lab. & Clin. Med. 11: 258, 1925. (5) *Gautier*: Quoted by Reis, E. (6) *Zeller, A.*: Ztschr. f. Geburtsh. u. Gynäk. 11: 56, 1885. (7) *Mainzer, F.*: Quoted by Keith, R. D.: Tr. Path. Soc. London 56: 365, 1905. (8) *Wertheim and Menge*: Quoted by Novak, Emil: AM. J. OBST. & GYNEC. 18: 449, 1929. (9) *von Franque*: Quoted by Novak, Emil: Ibid. 18: 449, 1929. (10) *Ries, E.*: Am. Gynec. & Obst. J. 8: 184, 1896. (11) *Fluhmann, C. F.*: AM. J. OBST. & GYNEC. 15: 1, 1928. (12) *Meyer, R.*: Quoted by Fluhmann, C. F. (13) *Graves, W. P.*: Gynecology, ed. 4, Philadelphia, 1928, W. B. Saunders Company, p. 548. (14) *Krompecher, E.*: Quoted by Fluhmann, C. F. (15) *Schmidt, H. R.*: Quoted by Fluhmann, C. F. (16) *Kaufmann, Edward*: Pathology for Students and Practitioners. Translated by S. P. Reimann, Philadelphia, 1929, P. Blakiston's Son and Company, 2: p. 1625. (17) *Kettle, E. H.*: Proc. Roy. Soc. Med. 12: 1, 1919. (18) *Herzheimer, Gottheimer*: Beitr. z. path. Anat. u. z. allg. Path. 41: 348, 1907. (19) *Murray, J. A.*: The Investigation of the Imperial Cancer Research Fund Reports 3: 159, 1908. (20) *Bowing, H. H., and Fricke, R. E.*: Am. J. Roentgenol. 21: 529, 1929. (21) *Norris, C. C., and Dunne, S. F.*: AM. J. OBST. & GYNEC. 32: 982, 1936. (22) *Healy, W. P.*: Am. J. Surg. 33: 474, 1936. (23) *Goldstine, M. T.*: S. Clin. North America 16: 13, 1936. (24) *Davis, Lincoln*: Tr. Am. S. A. 43: 290, 1925. (25) *Donald, Archibald, and Shaw, W. F.*: Proc. Roy. Soc. Med. 22: 307, 1928. (26) *Healy, W. P., and Cutler, Max*: AM. J. OBST. & GYNEC. 19: 457, 1930. (27) *Kelly, H. A., and Collaborators*: Gynecology, New York, 1928, D. Appleton-Century Company, pp. 600-607. (28) *Miller, C. J.*: An Introduction to Gynecology, St. Louis, 1931, The C. V. Mosby Company, 215 pp. (29) *Bowing, H. H., and Fricke, R. E.*: Am. J. Roentgenol. 40: 47, 1938. (30) *Stacy, Leda J.*: Radiology 5: 331, 1925. (31) *Broders, A. C.*: J. A. M. A. 74: 656, 1920. (32) *Idem*: Ann. Surg. 73: 141, 1921. (33) *Idem*: Ibid. 75: 574, 1922. (34) *Counseller, V. S., and Butsch, W. L.*: AM. J. OBST. & GYNEC. 31: 628, 1936.

Relevant Articles Not Referred to in the Text

- (1) *Bowing, H. H., and Fricke, R. E.*: Am. J. Roentgenol. 33: 50, 1935. (2) *Gellhorn, George*: AM. J. OBST. & GYNEC. 31: 37, 1936. (3) *Keith, R. D.*: Tr. Path. Soc. London 56: 365, 1905. (4) *Novak, Emil*: J. A. M. A. 108: 1145, 1937. (5) *Idem*: AM. J. OBST. & GYNEC. 18: 449, 1929. (6) *Palmer, A. C.*: Proc. Soc. Med. 21: 367, 1927. (7) *Rankin, F. W., and Broders, A. C.*: Surg. Gynec. Obst. 46: 660, 1928.

It is impossible to make a positive assertion concerning the origin of the mixed squamous cell carcinoma and adenocarcinoma of the uterus. It would appear most likely that it originates from a regenerative type of epithelial cell which is capable of forming either benign or malignant, squamous or glandular epithelial cells. Squamous epithelium has been demonstrated in the fundus of the uterus. Not infrequently small islands of squamous epithelium are found in glandular polyps arising from the region of the endocervix (Fig. 4). However, carcinomas can rarely be demonstrated as arising in such benign metaplastic epithelium. Furthermore, in none of the cases of mixed squamous cell carcinoma



Fig. 4.



Fig. 5.

Fig. 4.—Polyp arising from endocervix. There is a transition of columnar epithelium to benign squamous epithelium (metaplasia) (hematoxylin and eosin $\times 120$).

Fig. 5.—Squamous cell carcinoma of the endocervix. The acinus lined by squamous cell carcinoma on one side and benign columnar epithelium on the other (hematoxylin and eosin $\times 165$).

and adenocarcinoma of the fundus of the uterus could benign squamous epithelium be found in the endometrium. It would appear that the malignant squamous cells in mixed cell carcinomas of the uterus originate from glandular epithelium without the formation of benign squamous epithelium (Fig. 5).

SUMMARY

Twenty-eight cases of mixed adenocarcinoma and squamous-cell carcinoma of the uterus have been described. Eleven of these were located in the body of the uterus and 17 in the cervix. They form approximately 1 per cent of the entire group of uterine carcinomas. The symptoms and signs do not differ appreciably from those of the more common varieties of carcinoma found in the uterine fundus and cervix. Eighty-three per cent of the mixed adenocarcinoma and squamous cell carcinoma

A. H. Morse, 1912, reported a case so treated and found four more in the literature. He discusses these cases in detail with an analysis of each, besides his own, which terminated successfully with a live baby and mother. The first to do the operation for this complication was E. G. Montgomery, of Quincy, Illinois, who, in 1894, performed extramedian symphysiotomy. The child was delivered but died twenty minutes later from asphyxiation.

The second case he reported was in Leopolds Clinic by Kannegeiser, which ended fatally for the child. The baby was delivered by craniotomy. The conjugate vera in this case was estimated at only 7.25 cm.

The third and fourth were by O. Pankow in 1910. In Pankow's first case the diagnosis was face presentation posterior in a primipara. Twenty-seven hours had elapsed between rupture of the membranes and the operation. Open pubiotomy was performed and the patient was allowed to deliver herself four hours later. She suffered high fever with streptococcic endometritis, thrombosis of the left and right legs. The patient was discharged on the sixty-seventh day after a stormy convalescence.

Pankow's second case was in a primipara. Open pubiotomy again was done. Eight and one-half hours later the baby was delivered with forceps, was deeply asphyxiated and could not be revived. The patient was discharged on the twenty-fourth day.

Titus credits Morse with saying that Montgomery's case would have had a happier ending had the child been in better condition at the outset, and that Kannegeiser's patient had a conjugate vera of 7.25 cm. and the delivery would have been difficult with a normal presentation.

In Pankow's cases open pubiotomy was used, which, Morse says, according to Titus, is more likely to infection, as an open wound in the region of genitalia is present. Waiting eight and one-half hours before delivery probably contributed to the injury and asphyxiation of the child in the second case.

Titus, 1916, reviewed Morse's paper, added his own case, and found reference to two more in the literature, one by Jacobsen and another by Whitridge Williams, reported in his textbook with no detailed history.

Jacobsen's patient was a large primipara, in labor for thirty-six hours with a posterior face presentation. The child was in good condition. The open pubiotomy was performed, but a vesicovaginal fistula developed. The patient was discharged with her baby after a troublesome convalescence; her fistula not quite healed.

Titus' patient, a para vi, appears to be the eighth treated in this manner, with face firmly impacted and the chin posterior. Pubiotomy by Doederlein technique was done on the right side and delivery was effected with the chin still posterior. The child was asphyxiated but breathed readily upon resuscitation. There was no laceration or bladder injury. The puerperium was febrile and this was attributed to the pubiotomy wound, but later it was discovered that the patient had an active pulmonary tuberculosis. She suffered no disability from the operation and was released after thirty-nine days. The baby weighed seven pounds upon discharge.

I was able to find only one other case in the literature.

In 1927, M. M. Audibert and Galy Gasparrou reported a case of pubiotomy done by them for impacted posterior face presentation. The history of their case follows: A primipara, 30 years of age, normal size, entered the Obstetrical Clinic, September, 1927, was at term and had been in labor for fifteen hours. The face was engaged in right mentum posterior. Dilatation was 2 or 3 cm. Next day the membranes ruptured. There was dilatation 4 to 5 cm., and great edema of the cervix. Contractions were strong and regular. Morphine, 0.01 Gm., was given without results.

Under spinal anesthesia a saw was passed on the left side after the technique of Doederlein. There was a median anterior and posterior incision of the cervix. Forceps were applied and the face easily brought to right transverse, but here no further progress could be made. It was decided not to sever the pubis until there had been many attempts to deliver with forceps.

A male child was born after pubiotomy but died seven hours later. The autopsy showed cranial injuries. The patient was discharged on the thirteenth day, walked without difficulty, and had no diastasis of sacroiliac joints.

PUBIOTOMY IN IMPACTED MENTUM POSTERIOR PRESENTATION

WILLIAM P. SHARKEY, M.D., PORTLAND, ORE.

THE purpose of this paper is to report a case of impacted posterior face presentation, treated successfully by pubiotomy, and to review the subject with the idea of re-emphasizing the procedure as a method of treating impacted face presentation not suitable to any other form of treatment.

If the chin rotates anterior, as it does in the majority of cases, delivery usually can be accomplished through the birth canal, spontaneously, or by the judicious use of forceps. But with partial extension of the head and with the chin posterior the forehead reaches the pelvic floor first and rotates to the front.

Continued labor causes the presenting part to descend until the head, neck, and chest of the child are firmly impacted in the pelvic cavity. Further progress is impossible and death of the child and subsequent rupture of the uterus are likely, unless some suitable operative interference is instituted at once. This picture presents a most serious complication.

If the presentation is diagnosed before the engagement of the face, changing of the presentation may be tried or the maneuver of Schatz, Baudelocque, or Playfair-Partridge attempted. If conditions are suitable, version may be done. Cesarean section may be accomplished in most cases with excellent results.

Unfortunately these patients usually have been allowed to progress in labor until impaction has resulted. The membranes have ruptured hours before, and there have been attempts at delivery. Under these circumstances there are a limited number of procedures which recommend themselves as far as the safety of the mother and baby is concerned.

Low segment cesarean section would be difficult, as trouble is often encountered in a normal presentation in extracting the head when engagement has occurred. Such a procedure in impacted face presentation would be most difficult. The limited mobility of the presenting part and the necessary application of forceps from the occiput to the mentum would not facilitate easy extraction, and dragging the head from deep in the pelvis would court injuries to the child. Extension of the incision above the bladder reflection would defeat the purpose of the operation.

Extraperitoneal section would present similar difficulties besides being a far more formidable procedure.

The treatment usually suggested in the late editions of our standard textbooks for impacted face presentation is low segment cesarean section or craniotomy if the child is dead or dying. There is bare mention of pubiotomy.

Recent advances in the technique of cesarean section have narrowed the indications of pubiotomy to a limited field.

DISCUSSION

From observation of my own case, and reviews of cases I have found in the literature, it can readily be seen that these patients are poor surgical risks and pubiotomy lends itself admirably to their treatment. It is certainly unfair to condemn pubiotomy on its maternal and fetal mortality when its indications have been narrowed to the poorest of surgical risks. Guggenberger gives statistics in his treatise on face presentation and lists maternal and fetal mortality under all treatments in 47 operative cases. Sixteen cesarean sections were done with three maternal and two fetal deaths. Two of these sections were transperitoneal, and the patients died from peritonitis. One was extraperitoneal and the patient died from generalized sepsis. One pubiotomy was done in this series, which was successful for mother and baby.

In all of the 10 cases here reviewed for impacted posterior facial presentation, there has not been a single maternal death, though the fetal mortality is 50 per cent. This fetal mortality might have been reduced considerably had three of the patients not been allowed to deliver themselves spontaneously after pubiotomy.

We have been taught that posterior face presentation should be allowed to progress in labor, anterior rotation of the chin should be awaited to permit spontaneous delivery, and, failing in this, vaginal manipulations to change the presentation should be tried.

We also have been instructed that the mortality of the various types of cesarean section is increased in direct proportion to the length of labor and to the number of vaginal manipulations.

In view of all this, we must accept the operation of pubiotomy as an emergency procedure when the child is alive. It is more simple, less shocking and carries a lower maternal mortality than the former operation of any type in this condition. Between craniotomy and pubiotomy there can be no choice, as maternal mortality statistics alone would support the latter procedure.

It is not my wish to advocate pubiotomy in competition with low cervical cesarean section, but I do believe that pubiotomy has a definite indication in posterior impacted face presentation. The two procedures have no common indications. Only those cases unsuitable for cesarean section come into the pubiotomy category.

REFERENCES

- (1) *Audebert, M. M.*: Gaz. méd. de France 393, 1931. (2) *Audebert, M. M., and Estienny, E.*: Bull. Soc. d'obst. et de gynéc. 18: 672, 1929. (3) *Audebert, M. M., and Galy-Gasparrou*: Bull. Soc. d'obst et de gynéc. 18: 166, 1929. (4) *De Lee*: Principles and Practice of Obstetrics, ed. 6, Philadelphia, W. B. Saunders Co.
- (5) *Fitzgibbon, Gibbon*: Practical Mid-Wifery, London, 1923, J. & D. Churchill.
- (6) *Gousakoff, F.*: Rev. franc de gynéc. et d'obst. 30: 185, 1935. (7) *Morse, A. H.*: Surg. Gynec. Obst. 14: 1912. (8) *Neidermeyer, Albert*: Zentralbl. f. Gynäk. 59: 1352, 1935. (9) *Schumann*: Textbook of Obstetrics, ed. 6, Philadelphia, W. B. Saunders Co. (10) *Sureau, M., Walther, P., and Mahivat*: Bull. Soc. d'obst et de gynéc. 25: 223, 1936. (11) *Guggenberger, J. Khreninger*: Arch. f. Gynäk. 142: 197, 1930. (12) *Titus, Paul*: Surg. Gynec. & Obst. 23: 1916. (13) *Idem*: Management of Obstetric Difficulties, St. Louis, 1937, The C. V. Mosby Co. (14) *Tweedy, Wrench, and Solomons*: Practical Obstetrics, ed. 5, 1925, Oxford University Press. (15) *Williams, Whitridge*: Obstetrics, ed. 6, New York, 1936, D. Appleton-Century Co. (16) *Idem*: Am. J. Obst. 61: 1910.

The report of my case, which appears to be the tenth treated in this manner, follows:

Mrs. E. S., aged 30 years, primipara, entered St. Vincent's Hospital, May 23, 1938. Dr. R. A. Bissett, her physician, saw her early in the morning of May 24, made the diagnosis of posterior face presentation, and called me at 8:30 A.M. for consultation. She had been in labor thirty hours. He had made no attempts at delivery, but the patient's temperature was 100° F., and her pulse was 110, on admission.

She had been in labor at home all the preceding day, the membranes having ruptured before the onset of labor. At this time her pains were strong and regular, and there was some evidence of a contraction ring about 10 cm. above the pubis. The patient was exhausted.

The fundus measured 38 cm. The breach was in the fundus. The fetal heart was on the right side, midway between the umbilicus and anterior superior spine of ilium. The presenting part was fixed in the pelvis. The pelvic measurements were: Interspinous, 26 cm.; intercrystal, 31 cm.; external conjugate, 21.5 cm.; intertrochanteric, 34 cm.; biischial, 10 cm.; anteroposterior, 12 cm. The promontory could not be reached because of the presenting part.

Vaginal examination showed the cervix to be fully dilated and retracted. The face was presenting with the chin posterior to the right and well below the ischial spines. An unsuccessful attempt was made to dislodge the child, but not even the slightest mobility could be obtained with moderate upward pressure. It was evident that the face was firmly impacted. Nevertheless forceps were applied and an attempt made to rotate the head, so that the chin would be anterior.

A moderate amount of force was applied without producing the slightest tendency toward rotation. At this time a one-inch incision over the spine of the pubis was made. The superior border of the pubis was exposed on the left side. There being no pubiotomy needle available, it was necessary to use a large aneurysm needle. After catheterization, the finger-guided needle was passed back of the pubis. The left labium was pulled toward the center so that the point of the needle would emerge through the skin. A Gigli saw was threaded through the wound, beneath the pubis, and the bone was severed. A deep left lateral episiotomy was performed.

Assistants held the patient's legs on either side, making counter pressure so that the weight of the thighs would not cause too much separation of the bone ends. The separation obtained was 2 to 3 cm. Kielland forceps were applied and rotation was accomplished with considerable difficulty. The face was then delivered as a right mentum anterior. The baby boy showed no signs of asphyxia and breathed immediately. Its weight was 3,410 Gm. The patient showed considerable shock after the delivery. Her pulse was 130, weak, and thready. She was given 1000 c.c. of 10 per cent glucose, intravenously. There was no extension of the episiotomy wound and catheterization showed clear urine. A retention catheter was inserted and episiotomy and pubiotomy wounds were sutured without drainage. The pelvic girdle was strapped with eight-inch adhesive tape and the patient was placed in bed in a pelvic swing. Her pulse was 120 and temperature 100° F. until the eleventh day post partum. Some dark, sticky urine passed through the catheter on the first and second days, but the urine soon became normal in appearance.

On the seventh day, there was a small opening in the episiotomy wound, from which there was a purulent discharge. The wound healed by the twelfth day. The patient was allowed to be in a chair on the twenty-first day post partum. She walked on the twenty-third day with no limp and no disability. She was discharged from the hospital the same day. The baby was apparently normal, weighing 3,715 Gm. Although the head was still extended backwards as in the position at birth, it was freely movable, but tended to resume the backward position. At the end of two months this condition had remedied itself. The patient at the end of six months had no apparent disability from the pubiotomy.

TABLE I. VERIFIED CASES OF EXTRAUTERINE PREGNANCY ASSOCIATED WITH TUBAL TUBERCULOSIS

NO. OF CASES	YEAR OF REPORT	AUTHOR	AGE OF PATIENT	MARITAL HISTORY	TUBES PREGNANT	TUBAL TUBERCULOSIS	OUTCOME OF OPERATION
1	1896	Warthin	38	Married 13 years. Sterile	Left	Both tubes	Died tenth day post-operative
2	1898	Freericks	36	Married 6 years. Para iv	Left	Left	Not recorded
3	1900	Alexander and Moskowitz	25	Nulliparous	Left	Left	Recovery
4	1902	Anspach	31	Married 8 years. Sterile	Right	Right	Recovery
5	1904	Stein	24	Nulliparous	Right	Both tubes	Not recorded
6	1906	Resinelli	34	Para iii	Left	Both tubes	Not recorded
7	1910	Ferroni	36	Para iii	Right	Left	Not recorded
8	1911	Falco	24	Nulliparous	Left	Both tubes	Died postoperative
9	1913	Mühsam	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
10	1915	Bovin	34	Married 9 years. Sterile	Right	Right	Not recorded
11	1916	Kröner	41	Married 11 years	Not recorded	Both tubes	Recovery
12	1920	Müller	28	Para ii	Left	Both tubes	Died third day post-operative (sepsis)
13	1920	Schröder and Rau	41	Married 11 years. Sterile	Not recorded	Both tubes	Recovery
14	1922	Acconci	33	Sterile	Right	Right	Recovery
15	1928	Mossa	34	Married 5 years. Sterile	Right	Left	Recovery
16-19	1931	Martius (4 cases of Steuber)*	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
20	1931	Höppner	35	Not recorded	Left	Left	Not recorded
21	1932	Werhatzky	31	Not recorded	Right	Both tubes	Not recorded
22	1932	Therkelsen	32	Nulliparous	Right	Right	Died tenth day post-operative
23	1934	Stefanelli	22	Para ii	Not recorded	Same tube	Not recorded
24	1936	Schönberg	36	Not recorded	Right	Right	Recovery
25-26	1936	Tenney	24	Para i.	Left	Left	Recovery
			36	Married 10 years. Nulliparous	Left	Left	Recovery
27	1938	Reifferscheid	37	Married 5½ years. Sterile	Not recorded	Same tube	Recovery
28	1938	Limpach and Boy	32	Married 4 years. Sterile	Left	Left	Not recorded
29	1939	Stevenson and Wharton	37	Married 11 years. Sterile	Left	Both tubes	Recovery
30	1939	Tenney**	40	Married 20 years	Right	Right	Recovery
31	1939	Stein	29	Married 8 years. Nulliparous	Right	Right	Recovery
32	1940	Busby and Fisher	32	Married 5 years. Nulliparous	Left	Left	Recovery
33	1940	Bland†	30	Married 13 years. Para i.	Right	Right	Recovery

*Details not recorded.

**Personal communication ; case not reported in literature.

†Personal case.

TUBAL PREGNANCY ASSOCIATED WITH TUBAL TUBERCULOSIS

P. BROOKE BLAND, M.D., PHILADELPHIA, PA.

(From The Department of Obstetrics, The Jefferson Medical College)

NOTWITHSTANDING the belief that various sequelae of tubal inflammation are the most common causes of pregnancy within the Fallopian tube, the combination of tubal tuberculosis and tubal gestation is comparatively rare. In an exhaustive study of the literature, both domestic and foreign, I found, as outlined in Table I, only 32 cases of the dual condition recorded. This would seem to indicate quite clearly that, as a cause of extrauterine pregnancy, tuberculous disease of the Fallopian tubes is seldom responsible.

In a study of 55,000 surgical specimens in the laboratories of The Jefferson Medical College Hospital, from 1907 to 1939 inclusive, there were recorded 209 cases of tubal gestation. In none of these was tuberculosis observed. There were also recorded 38 cases of microscopic tuberculous salpingitis.

For the eleven-year period, from 1928 to September, 1939, inclusive, there were operated upon in the hospital 193 cases of various forms of extrauterine pregnancy or nearly 20 cases each year. None of these showed any evidence microscopically of tuberculous infection of the tubes.

Moreover, in a fairly active gynecologic practice extending over a period of many years, the clinical record herewith presented outlines the first case histologically demonstrated which I have thus far encountered.

The clinical and pathologic history of the patient whom I studied, bringing the total number thus far recorded to 33, is as follows:

Mrs. W. K. (CH-1079), aged 30 years. The family history is entirely negative for hereditary disease. The parents of the patient together with all sisters and brothers (4 sisters and 3 brothers) are living and well.

The patient has never had any serious disease. Her menstrual function was established at twelve, always regular, every thirty days, the flow lasting from four to five days, moderate in amount. At times it has been accompanied by slight pain. The last normal period occurred about May 1, and the preceding period thirty days previously.

The patient was first married at the age of 17. Two years later she gave birth normally to a full-term female child. There were no post-partum complications. She was married again at the age of thirty.

Present Trouble.—The patient was admitted to The Jefferson Medical College Hospital on the afternoon of July 3, 1939. She was discharged well on July 22, 1939.

Two weeks before coming under observation she experienced some uterine bleeding of a mild type. This was associated with considerable pelvic distress, and she believed the symptoms indicated an oncoming miscarriage. She was seen by her family doctor who made a tentative diagnosis of an incomplete abortion and, accordingly, admitted her to the Mercer Hospital, Trenton, N. J., for treatment. Shortly after her admission a therapeutic curettage was performed. She remained in the hospital for five days.

Following her dismissal from the hospital the bleeding recurred and continued "off-and-on" until she was admitted to the Jefferson Medical College Hospital on July 3. At this time, in addition to the uterine bleeding, she was suffering from severe pelvic pain. This was intensely aggravated during a bimanual examination, so much so that the patient developed profound shock.

The abdominal wall was hypersensitive and movement of the cervix was exceedingly tender. The posterior vaginal fornix was distended and almost convex. In the right side of the pelvic cavity an indefinite mass was felt. From the foregoing physical symptoms and signs, a provisional diagnosis of a ruptured tubal pregnancy was made.

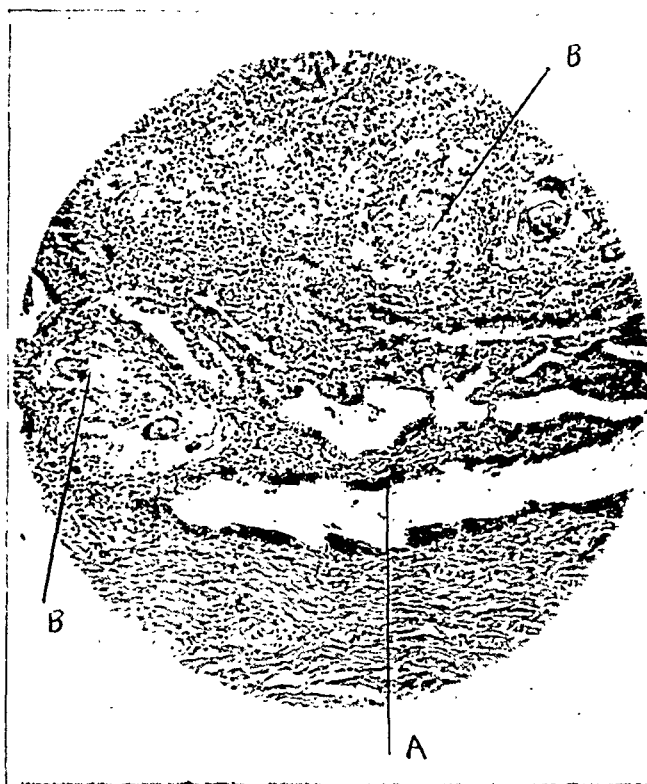


Fig. 2.—Section of a Fallopian tube, illustrating decidual reaction (A) and tubercles (B).



Fig. 3.—High power magnification of a portion of Fig. 2, illustrating a giant cell within a tubercle (A) and decidual tissue (B).

Blood examination showed red cells, 3,500,000; white cells, 8,000; and hemoglobin, 75 per cent. The urinalysis was negative, temperature 101° F., and pulse 82.

Operation.—Following admission she was immediately prepared for operation. Under gas-oxygen-ether anesthesia a diagnostic curettage followed by a posterior vaginal incision was performed. Through the incision a large quantity of fresh blood immediately escaped from the pouch of Douglas, thus confirming the diagnosis of a ruptured or aborted tubal gestation.

The patient was then placed in a modified Trendelenburg position and a mid-line incision was made. The abdominal cavity was inundated with fresh blood, and a large retortlike mass was found in the right side of the pelvis. This was delivered through the abdominal incision and resected. It was found to be a well-advanced tubal pregnancy, undergoing abortion. The left ovary and tube were examined, but were grossly not abnormal. The abdominal incision was closed, and

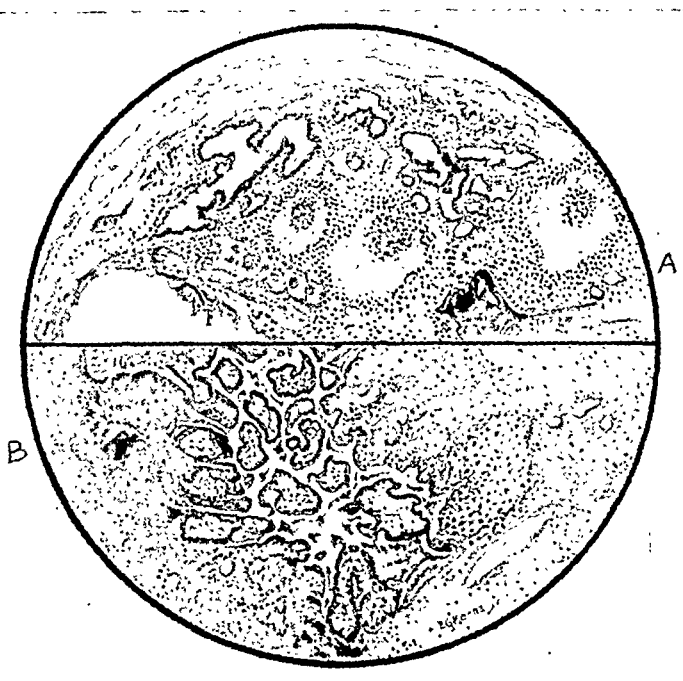


Fig. 1.—Illustration of tuberculosis and pregnancy in the same Fallopian tube. The upper half, A, illustrates the portion of the tube containing the tuberculous; and B, illustrates a portion of the tube containing the products of conception.

during closure, the patient received 300 c.c. of blood intravenously. This was repeated the following day and two days subsequently. During the first forty-eight hours, the condition of the patient was somewhat disquieting, but after that her recovery was wholly uneventful.

Follow-up Record.—Since her dismissal from the hospital, she has greatly improved. An x-ray of her chest made on Dec. 5, 1939, did not disclose any evidence of tuberculous disease, showing clear apices and normal peribronchial lung fields.

Pathologic Report.—*Specimen:* (Dr. Carl Bucher) Right Fallopian tube, ovary, and curettings. In diameter the Fallopian tube measured 6 cm. at the proximal end and gradually enlarged toward the distal end to form a dark, solid mass. The interior was mainly spongelike in consistency. There was no evidence of a true placenta or fetal structures. The ovary measured 3 by 2 by 2 cm. It was grayish in color and on section many small cystic cavities were observed.

Histology: 1. Several sections were taken from the Fallopian tube. The wall of the structure was edematous and hemorrhagic. On the inner surface there was considerable decidual tissue and in the lumen some "bits" of amnion as well as some chorionic villi. In addition, there was marked inflammatory reaction through-

THE RELATION OF OBSTETRIC COMPLICATIONS TO STERILITY*

RICHARD B. NICHOLLS, A.B., M.D., F.A.C.S., NORFOLK, VA.

THE purpose of this paper is to present the results of an investigation to determine the incidence and type of obstetric complications, including abortions, which occurred in 372 patients who have been treated for sterility in the private practice of Dr. C. J. Andrews and myself. All of these patients presented themselves to us with the primary complaint of sterility. Many of them made an inadequate number of visits to the office so that the results of their treatment could not be observed. This study is limited to those patients whose records revealed pregnancy or were followed by us for at least three years. This reduced the total number of cases reported to 118.

It is logical that women who have difficulty in becoming pregnant, provided the cause is not obvious, would possess certain inherent qualities which would affect the normal course, development, and delivery of their offspring. The normal physiology of the endocrine system is so delicately interrelated that maladjustments in its function produce alterations in the physiology, metabolism and growth of the woman to the extent that it is reflected in the shape of the pelvis, the maturation of the ovum, the production of secondary sex characteristics, the size of the uterus, tubes, and vagina, and upon the ovarian and pituitary secretions so necessary for the maintenance of pregnancy.¹ During pregnancy all of the endocrine organs are functioning at their highest efficiency and at delivery their climax is reached. Failure or partial failure in one or a combination of these factors either during pregnancy or at delivery may result in clinical manifestations, such as uterine inertia, post-partum hemorrhage, and premature separation of the placenta.¹ Experimental and clinical evidence is accumulating which points to endocrine dysfunction as a cause of pre-eclampsia and eclampsia.^{2, 3} Endocrine imbalance may make itself evident in the type of pelvic conformity which would result in various degrees of cephalopelvic disproportion, arrested descent of the head, posterior position, breech presentation and transverse lie.¹

For years ectopic pregnancy has been prominent as a complication in those patients who found it difficult to become pregnant.⁴ Ectopic pregnancies may have many causes, including damaged lumen of the oviducts, or underdevelopment of the lumen resulting from endocrine imbalance.

MATERIAL

Of the 118 patients studied, 9 aborted spontaneously and are listed separately, leaving 109 to be studied as to their obstetric complications. These 109 patients have been divided into two age groups: Those between twenty-one and thirty years

*Read at a meeting of the Norfolk County Medical Society, March 25, 1940.

out the tubal wall (Fig. 2). Sections taken from other portions of the tube showed an entirely different picture from that found in ordinary cases of tubal gestation. In these, there was observed extensive edema and hemorrhage together with an inflammatory reaction characterized by infiltration of the round cells. Most of these cells were lymphocytes. In many areas there were characteristic tubercles made up of a proliferation of epithelioid cells, giant cell formation, and an outer zone of inflammatory cells, chiefly lymphocytes (Fig. 3).

2. Sections taken from the ovary disclosed the presence of numerous cysts of varying size lined with low cuboidal epithelium. There was no evidence of tuberculosis in the specimen.

3. A microscopic section of the curetted tissue was made up almost exclusively of blood clots and necrotic material. There was not sufficient tissue to make a positive diagnostic statement.

Diagnosis.—(a) Tubal pregnancy, right; (b) tuberculosis of the Fallopian tube, right; (c) cystic ovary, right.

COMMENT

With tuberculosis accountable for 10 per cent or more of the cases of inflammatory disease of the uterine adnexa, it would seem logical to assume that pregnancy in the tubes, thus affected, should be more frequently encountered. The rarity of the combined condition is due chiefly, no doubt, first, to the invariably bilateral involvement of the tubes with tuberculous disease, second, to the widespread disorganization of the tubal walls with obstruction of the lumen and, third, owing to the inflammatory reaction in the tubal walls, to the prompt and early occlusion of their abdominal ostia.

Obviously, in cases of this character conception in the tubes is wholly impossible. It is only those cases of a localized type, with the tubal canal still more or less patent, that will permit ingress of the spermatozoa through the uterine and the ova through the fimbrial end and thus permit union to occur.

Finally, the relatively uncommon association of tuberculous salpingitis and tubal pregnancy may be partially explained on the ground that all tubal gestations are not, unfortunately, routinely studied in a microscopic way. If this course were generally practiced, it is likely that many more case histories would find their way into the literature.

REFERENCES

- (1) *Acconci, G.*: Folia Gynaec. 16-17: 253, 1922. (2) *Alexander, G., and Moskowitz, L.*: Monatschr. f. Geburtsh. u. Gynäk. 12: 182, 1900. (3) *Anspach, B. M.*: Univ. Penna. Med. Bull. 15: 159, 1902-1903. (4) *Bovin*: Monatschr. f. Geburtsh. u. Gynäk. 41: 492, 1915. (5) *Brisby, Eldon D., and Fisher, John H.*: AM. J. OBST. & GYNEC. 39: 125, 1940. (6) *Falco, A.*: Ann. di ostet. e ginec. 33: 637, 1911. (7) *Ferroni, E.*: Ann. di ostet. e ginec. 22: 1, 1910. (8) *Frank, Robert T.*: Gynecological and Obstetrical Pathology, ed. 2, New York, 1931, D. Appleton-Century Co., p. 322. (9) *Freericks, J. F. J.*: Zentralbl. f. Gynäk. 22: 1275, 1898. (10) *Höppner, H.*: Zentralbl. f. Gynäk. 55: 1269, 1931. (11) *Kröner, M.*: Arch. f. Gynäk. 105: 169, 1916. (12) *Limpach, L., and Boy, J.*: Gynec. et obst. 38: 359-361, 1938. (13) *Martius, H.*: Strahlentherapie 42: 471, 1931. (14) *Mossa, M.*: Clin. ostet. 30: 806, 1928. (15) *Mühsam, R.*: Therap. d. Gegenw. 54: 199, 1913. (16) *Müller, M.*: Arch. f. Gynäk. 112: 317, 1920. (17) *Reifferscheid, W.*: Ztschr. f. Geburtsh. u. Gynäk. 118: 38, 1938. (18) *Resinelli*: Ginecologie 3: 190, 1906. (19) *Schönberg, H.*: Ztschr. f. Tuberk. 75: 155, 1936. (20) *Schröder, R., and Rau, P.*: Zentralbl. f. Gynäk. 44: 972, 1920. (21) *Shober, J. B.*: Am. J. Obst. 38: 836, 1898. (22) *Simmonds, M.*: Arch. f. Gynäk. 88: 29, 1909. (23) *Stefanelli, C.*: Clin. ostet. 36: 283, 1934. (24) *Stein*: Ein Beitrag zur Lehre von der Aetiologie der Tubargravidität. Inaug. Dissertation, Giessen, 1904. (25) *Stein, Irving F.*: AM. J. OBST. & GYNEC. 38: 1068, 1939. (26) *Stevenson, C. S., and Wharton, L. R.*: Ibid. 37: 303, 1939. (27) *Taylor, A. M.*: Am. J. Surg. 24: 173, 1910. (28) *Tenney, B.*: New England J. Med. 214: 773, 1936. (29) *Therkelsen, F.*: Acta path. et microbiol. Scandinav. 9: 249, 1932. (30) *Warthin, A. S.*: Jahresb. über Geburtsh. u. Gynäk. 11: 694, 1897; also Med. News 69: 319, 1896. (31) *Werhatzky, N. P.*: Zentralbl. f. Gynäk. 56: 2946, 1932.

4. That more studies are needed for the exact correlation of specific obstetric complications to their related backgrounds of sterility.

5. That these findings should in no way deter the patient's desire for the correction of sterility, but should conversely increase the physician's vigilance in carefully handling any complication that might arise.

REFERENCES

- (1) *Mazer, Charles, and Hoffman, Jacob*: M. J. & Rec. 129: 90, 1929. (2) *Rakoff, A. A.*: AM. J. OBST. & GYNEC. 38: 371, 1939. (3) *Smith and Smith*: Ibid. 39: 405, 1940. (4) *Greenhill, J. P.*: Ibid. 33: 39, 1937.

605 MEDICAL ARTS BUILDING

SUBARACHNOID INJECTION OF ALCOHOL FOR THE TREATMENT OF PAIN IN GENITAL CARCINOMA

FRANK L. BAUER, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa)

THE importance of the treatment of intractable pain in patients with chronic progressive disease of various kinds is obvious. Since the subarachnoid injection of alcohol has received considerable attention because of the ease of its administration and its reported efficiency, it was decided to evaluate the results obtained from its use at the University Hospitals in patients with malignant disease of the female genitalia.

SUBJECTS

During the years 1933 to 1939 inclusive, 29 patients with incurable genital carcinoma received one or more subarachnoid injections of alcohol. The records of 22 were deemed sufficiently complete for the purpose of this study. The carcinoma originated in the cervix in 20, on the vulva in 1, and in the vagina in 1. A total of 27 injections was made, 5 patients receiving 2 treatments.

TECHNIQUE

All injections were made at or below the eleventh thoracic interspace, using recently distilled and carefully stored ethyl alcohol with no more than 6 per cent water.

Alcohol is lighter than spinal fluid and will overlies it in a more or less definite stratification. Its action is upon the unmyelinated pain and thermal fibers of the dorsal roots as they emerge from the cord and pass through the subarachnoid space.

During injection, the patient lies on the unaffected side. If the pain is bilateral, treatment must be repeated the following day with the patient lying on the other side. Accurate localization of pain-carrying segments is desirable, so that the initial injection will attack the desired fibers.

A number 19 or 20 gauge, spinal puncture needle is inserted into the subarachnoid space and 7.0 to 10.0 c.c. of spinal fluid withdrawn. Using a tuberculin type syringe, 0.5 to 1.5 c.c. of alcohol are injected during a three-minute interval. Rapid injection, movement of the patient during or shortly after injection, or introduction of air will interfere with the accurate stratification of the alcohol at the planned level. After the injection, the patient lies quietly on the side for sixty minutes and remains in bed for ten hours.

RESULTS

Detailed results of injections in the 22 patients in this series are summarized below. Of this group 9 received no or poor relief (lasting less

and those between thirty-one and forty years. There are 70 patients in the first group of whom 32 became pregnant and were delivered while 38 failed to become pregnant. Of the 32 who were delivered, twelve patients encountered an obstetric difficulty as listed in Table I. In the second age group, there were 39 patients of whom 16 became pregnant and were delivered while 23 failed to become pregnant. Of the 16 delivered, 7 encountered obstetric difficulties as shown in Table I.

To summarize, 372 case records were examined. Of these, 118 patients were studied, 9 aborted, 48 came to delivery, and 61 failed to conceive. Of the 48 delivered, 19, or 39.5 per cent, encountered major obstetric difficulties. Including abortions 57 conceived. If the abortions were added to the complications, it would increase the total number of complications to 28 or 49 per cent of those who conceived.

TABLE I

AGE	DELIVERED	FAILED	COMPLICATION
31-40	16	23	R.O.P., difficult forceps, stillborn
			R.O.P., Midforceps, long labor
			L.O.P., Midforceps, long labor
			Midforceps, slow dilatation, long labor
			Abruptio placentae, Porro cesarean
			Ruptured ectopic
			First breech, second central placenta previa, transverse position
39 cases			
21-30	32	38	Pernicious vomiting, therapeutic abortion at 2 months
			R.O.P., midforceps, Scanzoni
			R.O.P., midforceps, uterine inertia, hypertension
			R.O.P., midforceps, Scanzoni
			L.O.P., midforceps, moderate disproportion, difficult delivery
			Ruptured ectopic
			Ruptured ectopic
			Placenta previa marginalis
			Premature labor 7½ mo.
			Cesarean for disproportion
70 cases			Abruptio placentae, stillborn
			First ectopic, second disproportion-cesarean, third monster, fourth cesarean

TABLE II

Total records studied	372	
Case records used	118	
Abortions	9	
Exclusive of abortions	109	
Became pregnant and delivered	48	40.6%
Failed to conceive	61	
Total complications	19	39.5%
Including abortions	28	49.0%

Obviously this study is not of a sufficiently large series to be conclusive but it does suggest:

1. That the obstetrician, in giving prenatal care, must bear in mind the etiologic background of the individual patient's sterility.
2. That obstetric complications have a higher incidence in women who become pregnant following treatment for sterility.
3. That, due to the increased incidence of obstetric complications, expert obstetric judgment at delivery is needed.

fined to bed and the others soon will be. Therapy necessarily revolves around the relief of pain, which often is extremely severe. The alternatives are presacral sympathectomy, dorsal root resection or increasing doses of opiates, any of which may be objectionable. Since the injection of alcohol is a simple and often effective procedure, it is felt that in many cases the chance for relief outweighs the possibility of untoward effects.

SUMMARY AND CONCLUSIONS

Twenty-two patients with incurable and advanced genital carcinoma associated with severe pain were treated with subarachnoid injections of alcohol. It was found that:

1. When the pain distribution indicates involvement below the eleventh thoracic cord segment, the injection of strong alcohol into the subarachnoid space may occasionally give excellent relief, but more frequently the relief is incomplete or of short duration.

2. Such injections are often followed by serious permanent motor and sphincter disturbances.

3. There is an apparent correlation between the degree of relief obtained and the amount of the resulting motor and sphincter disturbance.

RESULTS OF INJECTIONS

All injections were made below the 11th thoracic vertebra. Unless otherwise specified:

"Transitory" refers to a period of seven days or less.

"Relief" refers to a period of more than seven days.

1. H-13254. Pain in lower abdomen, right hip, and leg. 1.75 c.c. of absolute alcohol. Urinary incontinence for 10 days, lower abdominal pain decreased, leg and hip pain persisted. No relief.

2. K-5223. Severe lower abdominal pain. Quantity of alcohol not stated. Immediate transitory numbness in left leg. No relief.

3. 38-16536. Deep pelvic and right groin pain. 1.5 c.c. of alcohol, repeated following day with patient lying on opposite side. Amelioration of pain for 3 days. Recurrence with full intensity. Permanent urinary incontinence and mild bilateral paresis.

4. H-93. Low abdominal pain more pronounced on right. 1.0 c.c. of 95 per cent alcohol with transitory numbness of the right lower extremity. No relief.

5. K-6773. Low abdominal, right hip and leg pain. 1.5 c.c. of absolute alcohol. Slight transitory improvement complicated by persistent motor paralysis.

6. K-8116. Low abdominal and bilateral leg pain. 0.75 c.c. of absolute alcohol, repeated following day with patient lying on opposite side. Transitory numbness and burning in legs. Numbness persisted. No relief from pain.

7. 38-22200. Right flank and leg pain which disappeared immediately following 0.9 c.c. of absolute alcohol but recurred in 2 days.

8. 39-9129. Deep pelvic, left groin, and leg pain. 0.7 c.c. of absolute alcohol, repeated following day with patient lying on opposite side. Transitory urinary incontinence and diminution of pain in left leg. Recurrence in 3 days.

9. 38-41459. Deep pelvic and right leg pain. 0.7 c.c. of absolute alcohol. Patient thinks she obtained very slight transitory improvement.

10. M-13116. Low abdominal and left leg pain. 1.5 c.c. of 95 per cent alcohol resulted in persistent difficulty initiating urination. Partial relief.

11. 38-28705. Deep pelvic and right leg pain. 1.0 c.c. of absolute alcohol gave transitory burning and numbness. There was an incomplete paralysis of right leg which slowly decreased after 10 days. Partial relief.

12. K-3036. Deep pelvic pain. 0.6 c.c. of absolute alcohol. Transitory numbness and motor paralysis of left leg lasting 36 hours. Slight relief.

13. P-6217. Severe lumbosacral pain. 1.0 c.c. of absolute alcohol. Permanent urinary incontinence and slight relief.

than seven days), 5 obtained indifferent relief persisting longer than seven days. The remaining 8 patients obtained good relief which lasted well beyond a week.

During injection there was usually a sudden burning sensation which gradually faded into a warm glow over the sensory distribution of the affected roots. Sensory test showed hypalgesia and lesser degrees of hypoaesthesia. Transient motor paralyses, sphincter disturbances and loss of the deep reflexes were frequently observed. As the alcohol diffuses into the spinal fluid, it becomes diluted and inactive. The leucocytes in the spinal fluid become temporarily increased, and there is often a mild febrile reaction which persists for twenty-four to thirty-six hours. In certain cases, in spite of adherence to a rigid technique, permanent motor weakness and sphincter disturbances will occur.

Since some of the patients were discharged shortly after receiving the injections, data on the late results were incomplete. Questionnaires were sent to the 10 patients in this group; but replies were received from only 3; 4 had died in the interval.

Eight of the 22 had motor paralysis, 6 had sphincter disturbances, and 5 had combined motor and sphincter disturbances, all of which lasted for more than three days. Five of the 8 with motor paralysis and 3 of the 5 with sphincter disturbances fell into the group of 8 patients who obtained good relief. In contrast, the group of 9 who obtained no or indifferent, transient relief included only one patient with combined motor and sphincter disturbances and one who suffered urinary incontinence.

DISCUSSION

To Dogliotti¹ is accredited the first report of subarachnoid injection of alcohol for the treatment of intractable pain. Since this time there have been many reports concerning its use, indications, and results. The various techniques are fundamentally similar. Stern² feels that the desirable alcoholic concentration in the spinal fluid is 30 per cent, and it has been established by experience that this is most efficiently achieved by injection of alcohol of approximately 95 per cent concentration by volume. Higher concentrations produce undesirable changes in the cord substance, and lower concentrations are ineffective. The closer to the end of the spinal cord injections are made, the less the volume of alcohol necessary to produce the effect. Below the third lumbar interspace, it is wise not to use more than 0.6 c.c., because at this level the size of the subarachnoid space in relation to the mass of nervous tissue is small and larger amounts affect the cord and give a cauda equina syndrome. This danger exists at any level, but when injections are made higher in the cord, there is a larger margin of safety.

From the results obtained in this series of patients, it is obvious that the injection of alcohol into the subarachnoid space is not a panacea for the severe pain produced by extensive genital carcinoma. The fact that over half of the motor and sphincter disturbances occurred in the 8 patients obtaining good relief is significant. Apparently these patients obtained relief because sufficient alcohol was injected to give a high spinal fluid concentration over a relatively wide area. This caused extensive destruction of both the anterior and posterior roots and probably changes in the cord itself that were clinically comparable to those seen in partial transverse myelitis.

When considering the possible deleterious effects of subarachnoid alcohol injection as a therapeutic measure for intractable pain, there are several mitigating factors. Most of the gynecologic patients who receive such treatment are in the late stages of carcinoma and have a very limited life expectancy. Some are already con-

Although Meigs and Cass, in 1931, called attention to solid fibroma of the ovary associated with ascites and hydrothorax as a clinical entity, other authors previously had noted these changes. Mapes² in 1909 noted ascites as a concomitant symptom of solid fibroma of the ovary, but did not mention hydrothorax. In 1913 Titus³ emphasized the presence of ascites in one-half of the cases of fibroma, and although his patient had chest findings, no mention of hydrothorax was made. The symptoms referable to the heart, i.e., dyspnea and orthopnea, he ascribed to the size of the tumors or to the ascites. In 1923, both Owen⁴ and Hoon⁵ independently described the presence of hydrothorax which disappeared following the surgical removal of the ovarian fibroma. Ascites was also noted by both authors.

CASE 1.—Mrs. G. M., a 45-year-old, white housewife, had been aware of the presence of a mass in her lower abdomen for about one year, during which time it had gradually increased in size. For about a year previous to the occurrence of her menopause she had noticed a prolongation of her menses and the passage of numerous blood clots in the flow. Following the menopause, however, there had been no further vaginal bleeding of any kind.

She stated that she was annoyed by a constant bearing-down sensation in her lower abdomen. She had also been troubled by a sacral backache for some time. During the two months preceding her admission to the hospital, she had lost twelve pounds in weight in spite of a fairly good appetite. At times she experienced edema of the feet and ankles, heart-consciousness, palpitation, slight dyspnea, and left thoracic pain on deep respiration.

The patient had been told that she had "thyroid and heart trouble." Her menopause had occurred one year previously, and there had been no postmenopausal bleeding.

Physical Examination.—The patient was a fairly well-nourished, well-developed, white female in no immediate distress. Her temperature, pulse, and respirations were normal. Her blood pressure was 120/70. The thyroid gland was not palpable. There was dullness in the lower chest bilaterally with some diminution in intensity of breath sounds on the left side. The left heart border was displaced laterally, and there was a soft systolic murmur at the apex. In the lower abdomen just above the symphysis pubis, a nontender baseball size, hard, smooth mass could be palpated. Vaginal examination revealed only the presence of the mass felt abdominally but yielded no additional information as to its origin or nature.

Laboratory Findings.—The blood and urine were essentially normal. The basal metabolic rate was -10 per cent. Electrocardiographs were reported as showing "evidence of extensive myocardial damage on a probable arteriosclerotic basis." Chest x-rays yielded the following: "There is a dense homogeneous shadow occupying the left base with its upper border definite and oblique and parallel to the anterior fifth rib. This shadow obliterates the diaphragm and costophrenic angle." Re-examination one week later confirmed these findings.

Preoperative Diagnosis.—On the basis of the above findings and a surgical consultation, a diagnosis was made of papillary adenoma of the ovary, probably malignant, with organic heart disease and left pleural effusion. Exploratory operation was advised.

Operation.—Operation was performed on Nov. 22, 1937, three weeks after admission to the hospital. There was free serous fluid in the peritoneal cavity. A large solid tumor of the left ovary was found. There were also several small uterine fibroids and a cystic mass in the left broad ligament. The right ovary was slightly enlarged and sclerotic. No enlarged lymph nodes nor any gross evidence of malignancy was seen. The left ovarian tumor and the cyst in the left broad ligament were removed.

The postoperative course was entirely uneventful and the patient was discharged on Dec. 4, 1937, the thirteenth day after operation, in good condition and much improved. When last seen in April, 1939, approximately sixteen months later, she was entirely well and had no complaints.

Pathologic Examination.—The specimen consisted of an ovary converted into a firm solid mass measuring 17 by 13 by 5 cm. The surface was smooth, purple-

14. P-8322. Deep pelvic pain. 0.75 c.c. of absolute alcohol resulted in transitory numbness with partial relief.

15. J-3773. Pain in left hip and leg. 0.75 c.c. of absolute alcohol. Immediate and complete relief.

16. K-8192. Pain in lower abdomen and right leg. 1.5 c.c. of absolute alcohol with immediate relief lasting for 6 months.

17. 39-12607. Pain in pelvis and left leg. 0.9 c.c. of absolute alcohol resulted in transitory burning and numbness. There was partial paralysis of right leg. Good relief during 30-day observation period.

18. K-9944. Deep pelvic pain. 0.6 c.c. of alcohol with immediate partial relief lasting 21 days.

19. 38-41607. Low abdominal and bilateral leg pain. 1.0 c.c. of 95 per cent alcohol, repeated following day with patient on opposite side. There was persistent bilateral incomplete motor paralysis and relief lasting 14 days.

20. 39-3812. Deep pelvic and right leg pain. 1.0 c.c. of 95 per cent alcohol. Persistent urinary incontinence and right motor paresis. Complete relief lasting 60 days.

21. 39-2564. Abdominal and right hip pain. 0.7 c.c. and 0.8 c.c. of absolute alcohol on left and right on successive days. Persistent urinary incontinence and bilateral paresis. Complete relief from pain.

22. 39-869. Pain in right leg. 1.0 c.c. of absolute alcohol. Transitory burning, numbness, and urinary incontinence. Paralysis of right leg but relief from pain during observation period of 7 days.

REFERENCES

- (1) *Dogliotti, A. M.*: Presse méd. 39: 1249, 1931. (2) *Stern, E. L.*: M. Rec. 143: 327, 1936.

FIBROMA OF THE OVARY WITH ASCITES AND HYDROTHORAX

A CLINICAL AND PATHOLOGIC STUDY WITH REPORT OF TWO CASES

EDWARD J. BOMZE, B.S., M.D., AND JACK D. KIRSHBAUM, M.S., M.D.,
CHICAGO, ILL.

(From the Department of Pathology, Cook County Hospital, and the Department of Gynecology, University of Illinois, and the Department of Surgery Northwestern University)

SOLID fibromatous tumors of the ovary are no longer considered rare nor of particular clinical significance. However, their occurrence associated with ascites and hydrothorax (frequently referred to as Meigs' syndrome) presents an extremely interesting clinical and pathologic entity, both as a diagnostic problem and as a condition which, in spite of a clinical picture of grave appearance, is almost magically relieved by surgery. Its recognition, therefore, is important to both clinicians and pathologists. This condition exemplifies an apparently benign tumor capable of producing effusions into two of the major body cavities (abdominal and pleural) without any detectable local or remote anatomic changes. Although this tumor is histologically benign, it produces a picture clinically simulating a pelvic malignancy with peritoneal and pulmonary or pleural metastases.

We are here reporting two such cases. One is fairly typical. The other is somewhat atypical, but illustrates the fact that a fatal termination may result if surgical treatment is too long delayed.

nuclei of these cells were long and flat, with pointed buds, and were rich in chromatin and quite regular in size and shape. Between these bundles there was a moderate number of dilated blood vessels. There were many areas of diffuse necrosis and hemorrhage. The necrotic and living tissues were separated by a narrow zone of edematous tissue. The tumor possessed an edematous capsule which was less cellular than the tumor and showed wide thrombosed blood vessels.

Anatomic Diagnosis.—Twisted large fibroma of the left ovary with hemorrhagic infarction and necrosis, acute glomerulonephritis, bilateral hydrothorax, ascites, and nodose goiter.

COMMENT

Case 1 is fairly typical of this syndrome in all its aspects and demonstrates the various factors brought out by Meigs⁶ and Meigs and Cass.¹ The patient had been hospitalized because of symptoms suggestive of cardiac failure. However, after the abdominal mass was discovered and x-rays revealed a hydrothorax, a diagnosis of malignancy of the ovary was made. This illustrates the value of emphasizing the importance of this syndrome. If the case had come to rest at this point on the conclusion that the patient was suffering from a hopeless condition of malignancy with metastases, the outcome would have been somewhat different from the satisfactory result finally attained. Operation had disclosed the actual cause of her symptoms.

Case 2 presents another aspect of the situation. Although the patient had a large ovarian fibroma, bilateral hydrothorax, and ascites, the picture was complicated by a pregnancy terminating at six months in eclamptogenic toxemia and spontaneous abortion. Death of the patient occurred two days after an exploratory operation in which the ovarian tumor and ascites were discovered.

In analyzing the events leading to her death, three possible mechanisms are to be considered. First, did the presence of a large ovarian tumor interfering with the progress of gestation and producing abortion, combined with the effects of toxemia and an exploratory laparotomy, cause her death? Second, did she die from the acute glomerulonephritis which was observed on microscopic examination? Third, one may consider as a cause of death an untreated Meigs' syndrome. That death may occur in this disease is brought out by Meigs⁶ who reports a case in which the patient died without operation.

Meigs' syndrome may be defined as a clinical entity in which a benign fibroma of the ovary is accompanied by a serous transudate in the peritoneal cavity and in one or both pleural cavities.

The condition may occur at any age after maturity, but is most often discovered in the early postmenopausal period. However, cases have been reported as occurring in patients 36 and 64 years of age.^{1, 7} The true frequency of occurrence is difficult to determine, since these cases are usually included in the group of ovarian fibromas in general. The incidence of ovarian fibroma is reported by various authors as ranging between 2 per cent and 4 per cent^{5, 8} of all ovarian tumors. Among our cases (autopsy and surgical material) fibromas make up 7.6 per cent of all ovarian tumors or 9.9 per cent of the benign group. According to Meigs and Cass,¹ in their review of the literature, they found that various authors report 13.7 per cent to 40 per cent of ovarian fibromas are accompanied by ascites.

Clinically in both of our cases there were features which suggested cardiac weakness with resulting circulatory disturbances. In Case 1 this is substantiated by the electrocardiographic findings. It is possible that in a patient who has a subclinical or compensated cardiac weakness in which the cardiac reserve is just sufficient to withstand the strain of the patient's activities, the added stress thrown on the heart by the pressure of the heavy ovarian fibroma, combined with its possible interference with pelvic and lower abdominal circulation, may be sufficient to produce a low grade cardiac decompensation, resulting in ascites and pleural effusion. This explanation is supported by the necropsy findings in one of the cases.

gray to yellowish tan, and in the capsule there was a single dilated and congested blood vessel. On sectioning, the cut surface was homogeneous light grayish tan and trabeculated. Microscopic examination showed the tumor to be composed of interlacing bundles of cellular fibrillar tissue. The nuclei were large, oval-shaped, and regular. There were no evidences of malignancy. The pathologic diagnosis made was benign cellular fibroma of the ovary.

CASE 2.—Mrs. R. S., 37 years old, colored, was admitted to the hospital on Sept. 11, 1930, complaining of pain in the right upper quadrant of her abdomen of three weeks' duration. The pain was sharp and constant, radiating to both sides of the back and had become more severe on the day of admission. On that day she had developed pains in the lower abdomen, recurrently cramplike in character, and resembling labor pains. She had been attending a prenatal clinic for some time and had been told that if the pains became more severe it would be necessary for her to enter the hospital. She stated that she had been aware of a palpable mass in her lower abdomen for at least four months.

The medical and surgical history were irrelevant. Her menses had been normal until the onset of her pregnancy. Her obstetric history included 9 pregnancies and 7 normal deliveries. She had two miscarriages and one of her babies had been a breech presentation delivered by "instruments."

Physical Examination.—The patient was poorly nourished and appeared to be in severe pain. Her temperature was 98° F.; pulse, 128; respirations, 24; and blood pressure 154/120. There was a nodular enlargement of the thyroid gland. The breasts were enlarged and colostrum could be expressed from both. The abdomen was distended asymmetrically with a large bulging mass on the right side which was hard and tense, and a smaller softer mass on the left side, the two together extending to the level of the xyphoid. Fetal heart tones could not be heard. On vaginal examination the cervix was found to be soft, the external os closed. There was a pitting edema of both lower extremities.

There were no significant laboratory findings.

On the basis of the above data a diagnosis of pregnancy with fibroids and eclamptogenic toxemia was made. However, the possibility of malignancy of the ovary complicating pregnancy was strongly considered.

Three days after admission, the patient delivered a dead six months' fetus, followed by spontaneous expulsion of the placenta. Examination showed a large hard rounded mass in the abdomen separate from the uterus. The patient's condition failed to improve and on Sept. 16, 1930, three days later, an exploratory laparotomy was performed under local anesthesia, and a large solid tumor of the left ovary with an unrecorded amount of free fluid was found. Because of the patient's poor condition, the mass was not removed. However, a biopsy was taken from it. Her condition remained poor following operation and on September 18, two days later, she died.

Autopsy.—(Performed by R. H. Jaffé.) Autopsy was performed on the day of death and the pertinent findings consisted of the following: There was a huge spherical firm tumor mass of purple gray color occupying the midportion of the abdominal cavity, displacing the liver, stomach, and transverse colon upward and the small intestines to the left and downward. This mass measured 29 cm. in transverse diameter, 27 cm. in vertical diameter, and 16 cm. in anteroposterior diameter. It weighed 7,150 Gm. The surface of the tumor was cloudy and covered by thin fibrinous tags. Its origin was the left ovary and its pedicle was formed by the Fallopian tube, ovarian ligament, and mesosalpinx, and was twisted through 330 degrees. There were dilated lymphatics in the mesovarium, and the veins were filled with light purplish red thrombi. On section, the cut surface was light, purple gray to dark purple and very firm, although it contained several up to 10 mm. cavities with a smooth lining and filled by a clear watery fluid. There was about 150 c.c. of cloudy, reddish brown fluid in the pelvis. The left pleural cavity contained about 700 c.c. of brownish fluid and the right about 50 c.c.

Microscopically, the tumor was composed of slender, spindle-shaped cells between which there were, at regular intervals, bundles of collagenous fibrils. The

The patient was subjected to complete roentgenologic investigation. The colon, gall bladder, esophagus, stomach, and duodenum were reported normal. The small intestinal series revealed all the small intestines situated in the right upper quadrant of the abdomen and in the epigastrium (see Fig. 1). The loops emptied readily. Roentgenograms of the chest revealed the diaphragm elevated bilaterally, but both lung fields were clear.

During the eight-day period of hospitalization, the patient remained distended but without pain. There was constant nausea. She was discharged upon her request on the eighth day.

The patient was re-admitted one week later. During this time the abdomen had increased in size, and she had developed extreme shortness of breath and a dry cough. Examination revealed the expansion of the thorax markedly restricted, especially on the left. Vocal fremitus and breath sounds were absent and the percus-



Fig. 1.

sion note was flat. The right lung field was clear. The heart was displaced to the left (Fig. 2). There was pitting edema of the lower legs. No change in the abdominal signs were noted except that a small ecchymotic area was observed surrounding the umbilicus (Cullen's sign). The urine was normal, the blood count showed an increasing anemia, the sedimentation rate was rapid, and the blood chemistry was normal.

Thoracentesis and paracentesis revealed grossly bloody fluid. Inasmuch as the presumptive diagnosis (pelvic tumor) was open to doubt, exploratory laparotomy was deemed advisable.

The patient was induced and maintained with evipal intravenous anesthesia because of the respiratory embarrassment. A large aspirating needle was introduced into the left thorax and approximately 500 c.c. of bloody fluid was first removed. A small suprapubic incision was then made. Upon opening the peritoneum, there was a gush of serosanguinous fluid. Palpation revealed the presence of a mass arising

SUMMARY

Two cases of benign solid fibroma of the ovary associated with ascites and hydrothorax are here described.

In both patients the left ovary was the site of the tumor, and the patients' ages were 45 and 37 years, respectively.

The hydrothorax was on the left side in one case and bilateral in the other.

A mild cardiac decompensation is suggested as the cause of the ascites and hydrothorax, as disclosed by the necropsy in the second case.

REFERENCES

- (1) *Meigs, J. V., and Cass, J. W.*: AM. J. OBST. & GYNEC. 33: 249, 1931. (2) *Mapes, C. C.*: Internat. Clin. 4: 205, 1909. (3) *Titus, R. S.*: Boston M. & S. J. 169: 381, 1913. (4) *Owen, A. W.*: Lancet 1: 1211, 1923. (5) *Hoon, M. R.*: Surg. Gynec. Obst. 36: 247, 1923. (6) *Meigs, J. V.*: Ann. Surg. 110: 731, 1939. (7) *Salmon, U. J.*: J. Mt. Sinai Hosp. 1: 169, 1934. (8) *Rhoads, J. E., and Terrell, A. W.*: J. A. M. A. 109: 1684, 1937. (9) *Weld, S. B.*: New England M. J. 218: 262, 1938.

GRANULOSA CELL TUMOR OF THE OVARY WITH HEMOPERITONEUM AND HEMOTHORAX*

REPORT OF A CASE

CLIFFORD J. VOGT, M.D., CLEVELAND, OHIO

(From the Department of Obstetrics and Gynecology, University Hospitals)

WITH the growing interest in granulosa cell tumors of the ovary, I wish to add this very interesting case to the literature. The presence of hemoperitoneum and hemothorax in association with any abdominal tumor must certainly carry a suspicion of a metastatic neoplastic process until definitely ruled out. In this case there was a rapid postoperative recrudescence to a normal physiologic and anatomic state, and the patient is symptom free after two years. This relatively short period of observation is not sufficient to comment on the relatively low degree of malignancy of granulosa cell tumors in general with any degree of confidence.

The patient, well developed, obese, 44 years old, first complained of a dull aching pain in both lower quadrants of the abdomen, more severe on the right, of two and one-half months' duration. The onset immediately followed a seven-day attack of dysentery. There had been constant nausea and anorexia and periodic vomiting for nine weeks. The patient had noted an increase in the size of the abdomen of one week's duration.

The patient had always been well. She was treated for sterility eighteen years previously, at which time a dilatation and curettage had been performed and a stem and Smith pessary was used for six months. Ten years ago the patient had an abdominal hysterectomy because of fibromyomas.

The menses had always been regular, every twenty-eight days, lasting three days, since the menarche at the age of fifteen until the removal of the uterus ten years ago. There have been no menopausal symptoms, remote or recent.

Upon admission the positive physical findings were: A tensely distended abdomen, but no tenderness and no masses palpable. A fluid wave was present. Pelvic examination revealed a normal cervix but the cul-de-sac and fornices were bulging, due to increased intra-abdominal pressure. No mass could be demonstrated. The lung fields were clear. The admission urine specimen was normal. The leucocyte count was 7,150, the erythrocyte count 4.22 million, and the hemoglobin 61 per cent (Sahli).

*With the permission of W. H. Weir and A. J. Beams.

Pathologic Report 1.—The specimen consisted of a cyst wall 28 cm. in diameter. The surface was smooth, gray pink, and glistening. The inner surface was covered by a rather thick layer of yellow-pink, somewhat granular tissue several centimeters thick. It had a tendency to be piled up in an irregular papillary manner. There was considerable fibrous tissue in the tumor mass.

Histologic examination of the tissue revealed a very cellular tumor growing in broad compact groups of cells. The individual cells were uniformly small and round or ovoid in shape, although in some areas they were elongated and of spindle type. The nuclei were vesicular and the cytoplasm abundant but poorly defined. Thin bands of connective tissue separated the masses of cells into poorly defined alveoli. There were a moderate number of mitotic figures. The tumor showed no differentiation. There was suggestive papilliferous arrangement in a few areas. There was no involvement of the capsule although small groups of cells were present just within the outer band of connective tissue of it. The type of neoplastic cell definitely resembled a granulosa type. *Diagnosis:* Malignant granulosa cell tumor (Fig. 3).

Pathologic Report 2.—The pleomorphism of the cells was not uncommon in granulosa cell tumors. There was no invasion of the capsule. The presence of a tiny amount of fat in the essential cells, together with their loose cytoplasm indicated a small amount of luteinization. The cellular parts of the tumor were devoid of reticulum; the lesion was therefore not a thecoma. The supporting tissue showed a rich reticulum which, in a few places, suggested the arrangement of theca interna. There was not adequate reason for considering this tumor as malignant. *Revised Diagnosis:* Granulosa cell tumor of the ovary with slight luteinization.

The lack of concurrence of opinion in the histopathologic examination of the tissue of this tumor is significant. It is obvious the variation in the two interpretations described above regarding the question of malignancy permits no compromise. It seems, therefore, that the criteria for malignancy in all granulosa cell tumors is not clearly defined; that there are instances in which these are subject to the element of individual interpretation, which may be variable. I quote Dr. Howard T. Karsner:* "There are several difficulties in the microscopic diagnosis of malignant granulosa cell tumors. With ordinary fixation it may be difficult to distinguish between true epithelium such as occurs in carcinoma, and granulosa cells. The matter of the diagnosis of malignancy is thus confused by the frequent lack of distinction between granulosa cells and epithelial cells. . . . The trabeculae of the (benign) granulosa cell tumor suggests an invasive growth, but they show a gradual merging with the enveloping capsule in contrast to the customary sharp distinction of invading carcinoma. The malignant granulosa cell tumor grows into and through the ovarian capsule and sections often show nodular masses associated with widespread hemorrhage and necrosis."

The frequency of mitoses is apparently not significant.

Hemoperitoneum and hemothorax, in the absence of known primary etiologic factors and in association with a "malignant" tumor, are usually presumptive evidence of a metastatic invasion of the peritoneum and pleura. In the absence of a proved metastatic involvement of these structures we are unable to explain the presence of the serosanguineous collection of fluid. It is well known however, that solid tumors of the ovary are often associated with abdominal ascites and even hydrothorax, yet the mechanism of the formation of these fluids has not been satisfactorily explained. In view of the rapid recovery of our patient I believe it is safe to dismiss the possibility of peritoneal or pleural carcinomatosis. It has, on the other hand, been observed that with the removal of the ovarian influence there is a temporary arrest, even regression, of the activity of metastatic as well as primary lesions.

Qualitative examination of the chest fluid for the presence of estrogenic substances might have revealed information valuable not only in the explanation of its etiology, but possibly in the further understanding of these tumors. Assuming a positive estrogenic titer to be present, ectopic secreting foci within the pleura are conceivable; their disappearance, or the disappearance in their activity, possibly following the removal of the ovarian influence.

*Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction, Transactions and Studies, College of Physicians of Philadelphia 1: 301, 1940.

from the pelvis. The incision was enlarged and an encapsulated, gray colored "meaty" tumor, approximately 25 cm. in diameter was found involving the left ovary. It was adherent in the cul-de-sac and to the posterior sheath of the left broad ligament. In attempting to free up the mass, the capsule was ruptured, and it was then removed piecemeal. The abdomen was washed with 8 liters of normal saline solution.

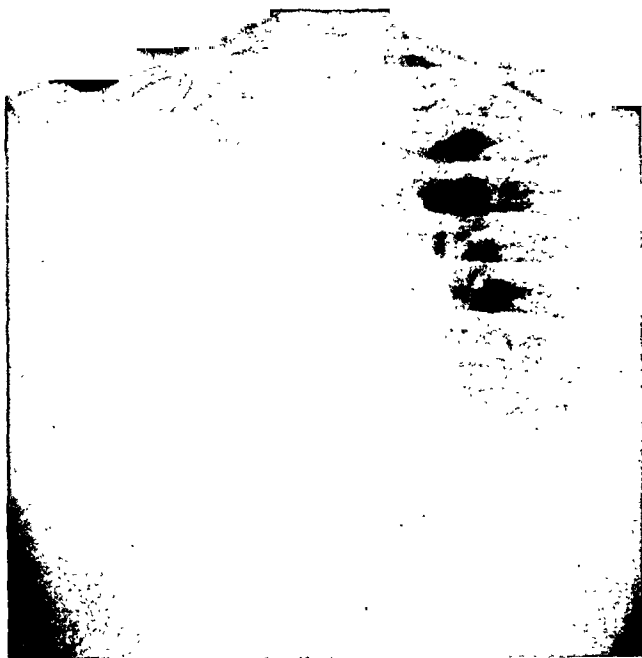


Fig. 2.

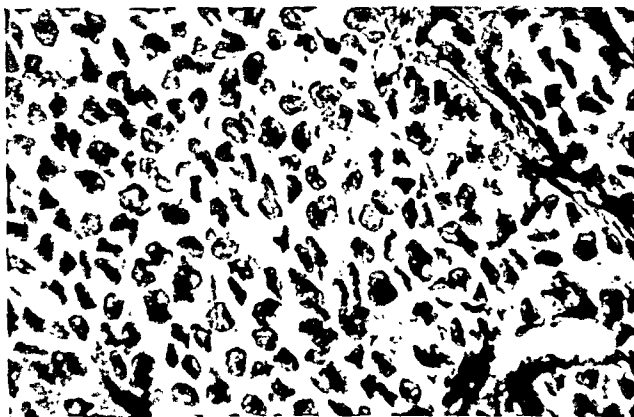


Fig. 3.

The postoperative course was uncomplicated. Physical signs referable to the left chest gradually disappeared and the abdominal ascites did not recur. Upon discharge from the hospital on the fifteenth postoperative day, there was good expansion of the lung and excursion of the thorax, and there was no evidence of remaining fluid.

The patient has been examined regularly since her discharge from the hospital and has been subjected to repeated fluoroscopic and roentgenologic examinations. There has been no evidence of recurrence by pelvic examination.

fibroids and was only slightly movable. A large rather firm and well-fixed mass filled the right lower quadrant. The inguinal lymph nodes appeared to be normal. The clinical impression was malignant ovarian tumor, fibroid tumors of the uterus, and hypertensive heart disease with early congestive failure.

Roentgenogram of the chest revealed the lung fields to be clear except for some congestion in both lower lobes. Also the cardiac shadow indicated a slight left ventricular enlargement. The patient was given digitalis for the congestive failure and the uterus, tubes, and ovaries were removed.

Tissue Examination.—The uterus measured 12 by 8 by 7 cm. The increase in size was caused mainly by a soft, well-circumscribed mass located in the fundus of the uterus. It measured 6 cm. in diameter and grossly resembled a fibromyoma with degenerative changes. On cross section, this mass was found to be composed of soft, moist, glistening white tissue in which there were numerous small irregular



Fig. 1.—Papillary carcinoma of the endometrium.

areas that were filled with clear light yellow fluid, giving the impression of edematous degeneration or sarcomatous change of a uterine fibromyoma. Several mural fibroid tumors without any degenerative changes were present in the other portions of the myometrium with the largest of these measuring 2 cm. in diameter. The endometrium just over the degenerated fibromyoma was soft, somewhat irregular, and measured 5 to 7 mm. in thickness. It grossly resembled a marked localized hyperplasia. The left ovary measured 2 by 2 by $1\frac{1}{2}$ cm. and consisted largely of an atrophic fibrous mass. The right ovary was enlarged because of a cyst which measured 8 cm. in diameter and contained a chocolate brown serous material. On the inner surface of this cyst there were several soft light yellow elevated areas which were about 1 cm. in diameter and 6 to 7 mm. in thickness.

Microscopic sections of the endometrium show an unrestrained growth of epithelial cells, having a distinct papillary formation with numerous proliferating stalks and buds (Fig. 1). Very few solid areas of these active epithelial cells are present. Under high power these cells are round to polyhedral and columnar in shape, vary somewhat in size, with large hyperchromatic nuclei, and have a moderate amount of clear cytoplasm. Mitoses are fairly numerous and very

SUMMARY

A case of granulosa cell tumor of the ovary associated with hemoperitoneum and hemothorax is reported. Although this case initially simulated a true malignancy, there has been no evidence during the past two years of observation which would substantiate this impression.

REFERENCES

Novak, E.: AM. J. OBST. & GYNEC. 28: 637, 1934. Schulze, M.: West. J. Surg. 47: 114, 1939. Dockerty, M. L., and MacCarty, W. C.: AM. J. OBST. & GYNEC. 37: 425, 1939.

10515 CARNEGIE AVENUE

CARCINOSARCOMA OF THE UTERUS

BYRON J. HOFFMAN, M.D., EMORY UNIVERSITY, GA.

(From the Department of Pathology, Emory University School of Medicine,
and the Robert Winship Clinic, Emory University Hospital)

EWING¹ collected 10 cases of carcinosarcoma of the uterus up to 1928 and in the same year Newell² found 20 cases reported. Since 1927 three cases have been reported in the English literature,²⁻⁴ one in French by Daniel and Lazaresco⁵ and one in German by Breiter.⁶

Saphir and Vass,⁷ in their review of the reported cases of carcinosarcoma, are not convinced that all of them are actually carcinoma and sarcoma. Of the 153 cases which they reviewed only three or four qualified as multiple neoplastic processes. Of 36 cases occurring in the uterus, they did not believe any to be true coexisting carcinoma and sarcoma. The most common sources of error in interpretation were based upon the suggestive appearance of sarcoma because of a marked stromal reaction to the invasion of carcinoma, the extreme variability of epithelial cells, especially when transitional or spindle forms were present, and the part which chronic inflammation may play in the production of pleomorphic cells resembling sarcoma. Therefore, these authors question the coexistence of carcinoma and sarcoma in the great majority of the reported cases.

CASE REPORT

Mrs. W. T. A., a white widow, 62 years of age, was admitted to the Emory University Hospital on July 16, 1939, complaining of an abdominal tumor, leucorrhea, and some vaginal "spotting" for the past two years. During the preceding eight years a slowly growing tumor mass had been noted in the lower abdomen, but there had been no discomfort until July 5, when she had a sudden severe pain in the left lower quadrant sufficient to cause her to go to bed and call a physician. Ice packs to the abdomen and the use of sedatives were followed by complete relief of the pain in twenty-four hours, with no recurrence after this attack. Her physician then advised hospitalization for the removal of her tumor.

Past History.—Menopause occurred thirteen years ago. No operative procedures had ever been performed, and she had always been in good health except for occasional shortness of breath during the past two years.

Physical Examination.—The patient was a well-developed and slightly obese white female in no apparent distress. Her temperature, pulse, and respiration were normal. The blood pressure was 170/110, and there was some cardiac enlargement of the left ventricular type. On abdominal palpation a large, firm, fixed tender mass was found almost filling the pelvis. Vaginal examination revealed a normal cervix with the uterus pushed to the left and enlarged apparently from the pressure of

chromatic fibroblasts or myoblasts that are grouped around the smaller vessels. At no place can there be seen the usual whorls of smooth muscle tissue and bundle formation usually seen in fibroids.

Postoperative radiation to the pelvis was carried out in the Winship Clinic of Emory University Hospital. Fifteen hundred roentgen units were given anteriorly over each lower abdominal quadrant and a like number posteriorly over each gluteal region at the level of the sacrum and lower lumbar vertebrae. The dosage was divided into 300 r. each day, by alternating successively at the four areas, with 200 kilowatts through a composite filter at a distance of 50 cm., and through a port 20 by 10 cm. At this time, three months after operation, no further metastasis has been found.

In the case presented, the myosarcoma and the papillary carcinoma of the uterus are believed to be two separate entities, that is, multiple primary malignant tumors, each having its own histologic characteristics. Since the predominant feature of this carcinoma is its papillary arrangement without any surrounding fibrosis, there is little reason to interpret the separate sarcoma as an extreme fibroblastic reaction to the carcinoma. Likewise there is no inflammatory change present which might serve as the cause for an extreme fibroblastic reaction.

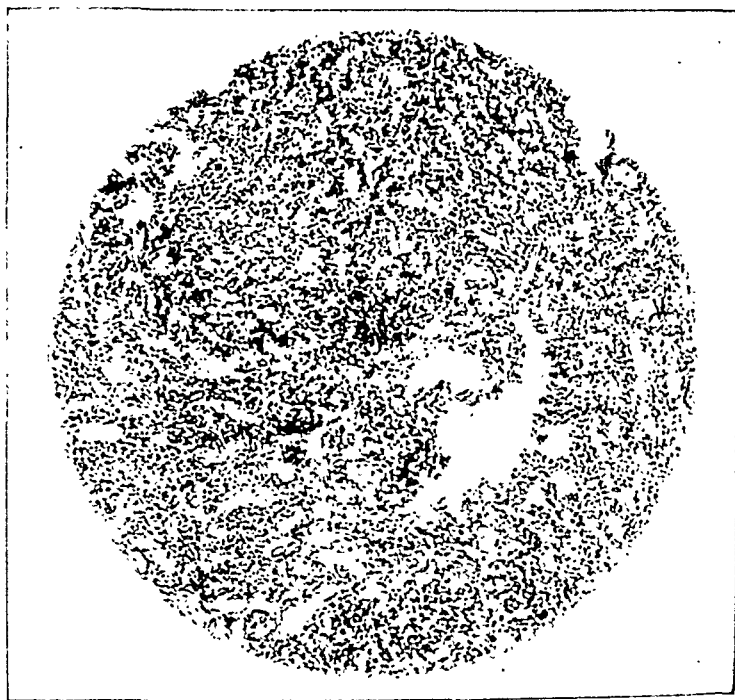


Fig. 3.—Small cell (myo-?) sarcoma in fibromyoma directly under the tumor of the endometrium.

The occurrence of myosarcoma of the myometrium and an overlying papillary carcinoma of the endometrium with ovarian metastasis is especially interesting from the viewpoint of the possible influence the myosarcoma or the fibromyoma might have had on the development of the adjacent endometrial carcinoma. This has been discussed by Ewing¹ as well as others.

SUMMARY

A case is reported in which there was a papillary carcinoma of uterine endometrium with metastasis to one ovary and a sarcoma in the adjacent fibromyoma.

little inflammatory reaction is present. Several small areas of endometrial glands, typical of adenomyoma of the myometrium, are present in this section. This same microscopic picture of disorderly epithelial hyperplasia in papillary formation prevails in the sections of the ovary taken from the soft yellow elevated areas of the cyst wall (Fig. 2). Very little actual glandular formation is seen in either of the tumor areas, being almost entirely papillary in type. The question arises whether these endometrial and ovarian tumors are separate papillary carcinomas, or whether it is a primary tumor in the uterus with ovarian metastasis, or possibly primary in the ovary with metastasis to the uterus. It is most likely that the carcinoma began in the endometrium and metastasized to the ovary. This is concluded from the appearance of such sections as seen in Fig. 1, which shows a small area of normal endometrium and when the lymphatic drainage of the uterus and ovary is considered. The lymphatic collecting channels of the uterus have their principal drainage from four or five vessels of the



Fig. 2.—Papillary carcinoma of the ovary.

fundus which pass laterally through the broad and suspensory ligaments of the ovary and follow the ovarian vessels to the lumbar and pre-aortic nodes. There are others which pass laterally with the uterine vessels to the iliac nodes, and some smaller ones that follow the round ligament to terminate in the inguinal nodes. The lymphatics of the ovary follow the ovarian blood vessels to end in the lumbar nodes. Thus the chance of metastasis of a primary tumor of the ovary to the uterus is quite unlikely and even though this did happen through aberrant lymphatic channels or retrograde extension, the ovarian metastasis should occur on the serous surface of the uterus rather than in the endometrium.

Microscopic sections of the large mural fibroid consist in part of masses of small deeply stained undifferentiated cells (Fig. 3) which under high power are seen to be round or polyhedral in shape with very little cytoplasm. A moderate number of mitoses are present and such areas are interpreted as being true myosarcoma. In other areas of this same section there is a considerable amount of glistening hyaline tissue in which are numerous islands of well-preserved hyper-

REFERENCES

- (1) *Ewing, J.*: Neoplastic Diseases, ed. 3, Philadelphia, 1928, W. B. Saunders Co. (2) *Newell, Q. U.*: AM. J. OBST. & GYNEC. 17: 191, 1929. (3) *Coweles, G. E.*: Ibid. 24: 200, 1932. (4) *Moench, L. M.*: M. Clin. North America 14: 687, 1930. (5) *Daniel, C., and Lazaresco, Mme.*: Rev. franç. de gynéc. et d'obst. 30: 883, 1935. (6) *Breiter, R.*: Zentralbl. f. Gynäk. 62: 2218, 1939. (7) *Saphir, O., and Vass, A.*: Am. J. Cancer 33: 331, 1938. (8) *Haney, W. F., and Hamilton, T. D.*: Edinburgh M. J. 42: 337, 1938. (9) *Dixon, C. F., and Dockerty, M. B.*: AM. J. OBST. & GYNEC. 39: 128, 1940.

RIGHT UTERUS UNICORNIS ASSOCIATED WITH RENAL AGENESIS

HERBERT J. SCHATTENBERG, M.S., M.D., AND JOSEPH ZISKIND, M.D.,
NEW ORLEANS, LA.

(From the Department of Pathology, Tulane University School of Medicine and the
Charity Hospital of Louisiana)

TRUE uterus unicornis is a very uncommon abnormality and its association with renal agenesis is very rare. This anomaly must be differentiated from the so-called unicornuate uterus with a rudimentary horn. The latter condition is seen more often than the former and is also sometimes associated with unilateral renal agenesis. Schumacker¹ was able to find only 28 cases in the literature, of true unicornuate uterus. Since his review no cases have been reported.

It is during the sixth week of development that the Müllerian ducts are seen and they are located at the ventrolateral aspect of the Wolffian ridges. In approximately one week's time, each Müllerian duct contacts the cloaca and eventually a lumen develops. In the male, these ducts begin to atrophy in about the third month while in the female they continue to develop. The proximal portions of these ducts form the Fallopian tubes and the distal portions unite to form the uterus and vagina. The medial wall formed by the fusion of both Müllerian ducts degenerates and a single uterus and vagina are formed. Condensation of the mesenchyme within the inguinal folds of peritoneum gives rise to the round ligament.

It is by a deviation from the normal or arrestment at certain stages in development of the Müllerian ducts that various types of malformations of the uterus arise. Unilateral or bilateral failure of development may occur in the first month. A double uterus and vagina (uterus didelphys) may form during the second month because of the failure of fusion of both sides. There may be arrestment of development on one side giving rise to a rudimentary horn. Uterus bicornis may form during the third and fourth months because of incomplete fusion of the two Müllerian ducts or an arcuate uterus may develop. A persistence of the septum or a single or double cervix may develop. The only malformation that occurs after the fifth month is an arcuate uterus. It is also possible that a uterus may appear normal externally but there may be a persistent septum. This septum may or may not continue into the vagina giving rise to the uterus septus duplex or uterus and vagina septus duplex.

Schumacker¹ noted that the patient's ages varied from one day or less to seventy-six years. The anomaly was present in about 60 per cent of cases on the left side and in 9 cases the ovary and tube were completely absent on the defective side. In eleven other cases the ovary was ectopic and located above the pelvic brim. The ovary in general was usually longer and narrower on the

The left kidney and ureter were completely absent. There was no left ureteral opening in the urinary bladder. The uterus was a small unicornuate body, firm in consistency and measured $6\frac{1}{2}$ cm. by 3 cm. by 2 cm. No definite point of demarcation was noted between the fundal and cervical portions. The uterus lay obliquely to the right in the pelvis with its upper end directed toward the right. The broad ligament on the right was small but intact. The uterine vessels were small in size. A well-developed round ligament ran from the fundus to the internal inguinal ring. The right tube arose from the cornual end and measured 8.5 cm. by 0.5 cm. A small subserosal cyst measuring 2 mm. in diameter was present in its midportion. The fimbriated extremity was open. The right ovary measured 3 by 1.5 by 0.7 cm. It appeared grossly normal and the ligaments were normal. On the left side there was no broad ligament or uterine vessels. The round ligament was thick and well developed. The left ovary was larger than the right and measured 4.5 by 1.8 by 0.7 cm. It lay vertically close to the internal abdominal ring. Its vessels entered at the upper end. From its caudal extremity a thin ovarian ligament extended toward the internal inguinal ring. At its upper border was a small cystic area measuring 1.5 cm. by 1 cm. Attached to it was a hydatid of Morgagni. This was the Fallopian tube, both ends of which were closed. Both ovarian veins entered directly into the inferior vena cava.

A case of true right unicornuate uterus associated with renal agenesis is reported, making the thirtieth case reported in the literature.

A short description of the embryology and the possible developmental anomalies likely to occur is noted.

The patient bore two children without difficulty but developed a chronic pyelonephritic contracted kidney and died in uremia.

REFERENCE

- (1) *Schumacker, H. B.*: Arch. Surg. 37: 586, 1938.

CONGENITAL ATRESIA OF THE UPPER TWO-THIRDS OF THE VAGINA AND CERVICAL OS WITH HEMATOMETRA

EDWARD A. FLEMMING, M.D., AND HARRY L. KAVA, M.D.,
FLUSHING, N. Y.

(From the Gynecological Service, Queens General Hospital)

ACCORDING to the accepted embryologic authorities, the tubes, uterus, cervix, and vagina are constructed by the fusion of the Müllerian ducts and the hymen is formed by the union of the caudal ends of the Müllerian ducts and urogenital sinus. Some embryologists as Frazer¹ and Jordan² claim that the vagina has a dual origin, the upper two-thirds arising from the fusion of the Müllerian ducts, and the lower one-third from a coalescence of the upper portion of the urogenital sinus and the lower ends of the Müllerian ducts. Dean Lewis³ cites a case where there was complete absence of the tubes, uterus, cervix, and upper two-thirds of the vagina, while the lower one-third of the vagina and the external genitalia were present and normal, clinically proving the double origin of the vagina.

Robert Meyer⁴ only recently wrote illuminatingly on the development and pathology of congenital closure of the vagina through a detailed study of a markedly atretic vagina in a girl fourteen days old who had come to autopsy. His former and present studies have revealed that the Müllerian ducts reached the urogenital sinus where they ended blindly; that the Müllerian ducts do not break through the urogenital sinus but instead, the sinus epithelium penetrates the

REPORT OF CASE

M. R., a white married female, aged 32 years, was first admitted to the hospital on June 24, 1939, complaining of dyspnea and edema of the feet. Following her second and last pregnancy seven years ago, the patient noted occasionally edema of the eyes and face, most marked in the mornings. About one year before admission she developed dependent ankle edema and dyspnea which became progressively worse. She complained of occasional attacks of precordial pain and palpitation. During the last two weeks her appetite was poor. She had been married ten years and had two children, one seven and the other nine years of age.

Physical examination revealed a poorly developed and nourished, anemic, white female lying quietly in bed. The blood pressure was 254/148, temperature 99° F., pulse 90, and respirations 20. The tonsils were atrophic. A few crepitant rales were heard at both bases. The heart was questionably enlarged. P₂ was greatly accentuated and harsh. M₂ was split. No murmurs or friction rubs were heard. The liver was palpable to the level of the umbilicus. There was moderate pitting edema of the legs and ankles. The blood Wassermann was negative. The hemoglobin was 55 per cent, and the red blood cell count was 2,730,000. The urine was yellow and acid. The specific gravity was 1.005. Albumin was present and the sugar was negative. Microscopic examination revealed numerous epithelial cells and 3 to 8 pus cells per high power field. A Fishberg test revealed a variation of specific gravity from 1.007 to 1.010. Blood chemistry on June 26, 1939 showed a urea of 91 mg., creatinine of 6.66 mg., and a glucose of 95 mg. per 100 c.c. of blood. On June 29 a repeat blood chemistry showed a urea of 100 mg., a creatinine of 11.4 mg., and a sugar of 117 mg. per 100 c.c. A stool examination was positive for blood. An electrocardiogram showed definite evidence of myocardial disease. X-ray examination of the chest showed the cardiac shadow to be apparently enlarged and the borders were obscured by edema at the bases of the lungs. The patient was treated with transfusions, digitalis and a low protein and salt-free diet. She was discharged unimproved on June 29, 1939. The patient was readmitted on July 31 with an aggravation of previous symptoms. Her blood pressure was 170/110 and she was in marked respiratory distress. Moist rales were heard at both bases of the lungs up to the level of the eighth rib posteriorly. The heart was enlarged to the left and to the mid-axillary line in the sixth interspace. No murmurs were heard. The liver was enlarged 8 cm. below the costal margin, and there was evidence of fluid in the abdomen. The lower extremities showed moderate pitting edema extending up to the knees. Urine examination showed a specific gravity of 1.006, albumin was marked, sugar and acetone were negative, and the microscopic examination showed occasional white blood cells but no red blood cells. The blood urea was 120.4 mg., the creatinine 9.45 mg., and the glucose 136 mg. per 100 c.c. She was treated with concentrated glucose and other diuretics. Her condition became gradually worse. She developed a pericardial friction rub, went into coma and died on Aug. 15, 1939.

Autopsy Report.—The body was that of an underdeveloped and undernourished white adult female. The mouth showed poor oral hygiene. A decubitus ulcer measuring 2 cm. by 3 cm. was present over the sacrum. Moderate pitting edema of the feet, ankles and legs was noted. The main pathologic findings were intraperitoneal and intrapleural fluid accumulations. The lungs showed a few patches of bronchopneumonia. The heart was moderately enlarged and much fibrin was present on both pericardial surfaces. The spleen and liver were congested. The right kidney weighed 45 Gm. It was normal in position. The renal artery was patent but small in size. The capsule was thickened and adherent to the cortex. On stripping the capsule, the cortical surface was found to be roughly granular. At about its midportion, a large depressed scar was noted. The consistency was firm. The cut surface showed a markedly narrow cortex. The corticomedullary junction was indistinct. The medullary portion was narrowed. The pelvic mucosa was smooth and gray in color. The pelvis was dilated. The ureter was patent throughout. The urinary bladder was natural.

Sinai Hospital, New York City, 10 of which were due to hymenal atresia, the rest were acquired postpubertal due to a definite etiology.

Jackson⁹ reported a case of a girl 14 years old who had never menstruated and who complained of lower abdominal pain. A rectoabdominal examination revealed a cystic pelvic mass. At the first operation a left salpingo-oophorectomy was performed for a chocolate cyst; four weeks later she was re-operated upon for similar complaints and the uterus was found large and cystic. By dissecting the rectovesical septum, the tense mass was encountered and incised with escape of old blood. Jackson believes the hematometra was present at the first operation.

Mayer¹⁰ reports a case of a girl 18 years old who had never menstruated and complained of lower abdominal pain. The hymen was open, the vagina extended for 2 cm., and rectal examination revealed the uterus to be enlarged. At operation the uterus at the lower half was distended and a supravaginal hysterectomy was performed.

Gillespie and Davison¹¹ report a case of a girl 13 years old who had never menstruated and who complained of lower abdominal pain. Rectoabdominal examination revealed a pelvic mass. A bilateral salpingo-oophorectomy was performed for blood cysts, four months later she was re-operated upon for the same complaints, and a supravaginal hysterectomy was performed for a bulging mass in the lower half of the uterus. After closure of the abdomen the vagina was found to end blindly.

Baer¹² reports a case of a girl 16 years old who had never menstruated. The vagina ended blindly about 2 cm. above the hymen. The rectoabdominal examination revealed a pelvic mass. The rectovesical septum was separated and the pelvic mass opened through the "vagina," with escape of old blood.

Gemmell¹³ and Fothergill¹⁴ also reported a case each of hematometra due to atresia of the upper two-thirds of the vagina, for which they performed a supravaginal hysterectomy.

CASE REPORT

E. D. (76583) was admitted to the Gynecological Service of the Queens General Hospital, Sept. 12, 1938. She was 15 years of age and complained of amenorrhea and lower abdominal pain. Her mother died of pulmonary tuberculosis at the age of 33.

In the summer of 1937 she was suddenly seized with a severe lower abdominal pain which ceased spontaneously after about two hours. At that time she noted a slight swelling of the abdomen. Throughout the year she had about ten intermittent identical attacks at irregular intervals, the last one occurred during the week of Aug. 27, 1938.

Patient appeared about 15 years of age, was poorly nourished, had a poor hemic component and showed multiple acneiform eruptions of the skin. In the right lower quadrant of the abdomen there was an orange-sized swelling which was mobile and cystic and seemed to be attached to a pelvic viscus. The external genitalia were normal and the hymen was open. The vaginal introitus admitted the tip of the finger and ended in a blind pouch about 2 cm. above the hymen. Rectoabdominal examination revealed a tense semifirm enlargement of the uterus and the right adnexa were definitely thickened.

Under evipal anesthesia, the vagina was entered for about 2 cm. and by blunt dissection the rectovesical tissue was separated until the full length of the finger could be admitted. No cervix could be marked out. The mass was now clearly defined, being posterior and not filling the cul-de-sac. With pressure on the mass from above, the mass was punctured with a large needle passed through the posterior "fornix" and 1 c.c. of thick dark blood was obtained. The impression was that we had a case of atresia of the upper two-thirds of the vagina, atresia of the external os, effacement of the cervix with hematometra. Four days after this blunt dissection of the vagina, a pneumoperitoneum was obtained which revealed an enlarged mass protruding from the true pelvis and diagnosed as a dilated uterus. She was again examined under anesthesia and a small speculum entered the vagina with ease. Probing for the cervix was a complete failure.

Müllerian ducts at the junction of the latter and the urogenital sinus; that the sinus epithelium displaces the Müllerian epithelium and matures to squamous epithelium; that if the vagina from the Müllerian ducts was first a tube, the tube becomes a solid cord filled by sinus epithelium whose inner cells undergo dissolution with a resultant re-formed tube. The substitution of the Müllerian epithelium by sinus epithelium arises at the meeting of both epithelia, Müllerian and sinus. If through a defect, the Müllerian ducts at the lower ends do not reach the sinus epithelium, the latter cannot penetrate into the Müllerian ducts. If one Müllerian duct shows such a defect, then only one-half of the vagina is penetrated by sinus epithelium. What occurs with the Müllerian epithelium of the closed side of the vagina depends upon the presence of a communication in the vaginal septum between the two halves of the vagina, and in such a case the normal sinus-vaginal epithelium would penetrate through the septum opening. If there is no septum communication between the two halves of the vagina there should be no possibility to substitute the Müllerian epithelium, then only would it show if the Müllerian epithelium itself is capable of building squamous epithelium. Meyer has shown, when there is persistent Müllerian epithelium, this epithelium will ripen into mucous membrane as it does in the cervix. This explains the presence of mucous epithelium, glands, cysts, and adenomas of the vagina on an embryologic basis. Autopsy specimens from the fourteen-day-old girl with atresia of the vagina showed both squamous and mucous epithelium. But atresias may originate not only because of faulty development but also after substitution of the Müllerian by sinus epithelium.

Atresia of the vagina may be congenital or acquired. Nagel and Veit, referred to by King,⁵ believe that all types of atresias are acquired, because atresia of the vagina cannot be present with normally developed internal genitalia. They and King believe that before birth or early in life, as a result of gonorrhea, acute febrile diseases, irritating urine or irritating discharges associated with malnutrition and lowered resistance, ulceration and apposition of the vaginal walls may occur, with the resultant atresia of the same. Taussig in discussing King's paper rightfully denies that some form of vulvovaginitis is a prerequisite for atresia of the vagina. Clinically, Taussig's observations are the experiences of most of us, for gonorrheal and other nonspecific vaginitis is not infrequent in childhood, yet so few atresias subsequently develop or are found. He concludes that most prepubertal atresias are congenital and their presence is noted after puberty after symptoms arise.

Since congenital atresia of the vagina is possible, one should differentiate between such atresia and absence of the vagina. In the presence of an open hymen with a dimpling of about 2 cm. above the hymen with closure of the upper two-thirds of the vagina, shall we refer to such closure as atresia or absence of the vagina? Surely, to differentiate the two anatomic conditions one would have to section the rectovesical septum and examine histologically for the presence of fibromuscular tissue alone as it should occur in absence of the vagina or mixed with squamous or mucous epithelium or both as it should occur in atresia of the vagina. But such section of the rectovesical septum is not practical during an operation. However, clinically with a congenital atresia of the vagina one finds full development of the internal genitalia, and with absence of the vagina, there are other evidences of lack or malformation of the Müllerian ducts.

There are comparatively few cases reported in the literature of atresias of the upper two-thirds of the vagina with full development of the internal genitalia. Gemmell⁶ was able to find only 14 cases in the literature up to 1926. I have been able to collect 6 other similar anatomic cases besides our own.

Most of the atresias reported are atresias of the hymen, the complete vaginal canal being present. It is interesting to note that Brown⁷ collected from the London Hospital 50 cases of congenital retention of menses during a period of twenty-one years. Forty-one of the 50 patients showed the atresia at the hymen, only one near the cervix. Bernstein and Walters⁸ reported 19 patients with hematometra, in the twenty years from 1917 to 1937, admitted to the Mount

stripped down from the uterus and a longitudinal incision was made anteriorly and low in the uterus. A finger was inserted through this incision into the fundus and directed downward, meeting with an obstruction which was identified as internal os, and with dilatation of this os there was a back flow of about one-half pint of old blood. The finger in this lower cavity did not identify the cervix nor the external os but rather a smooth dilated cavity below the internal os with most of the bulge posteriorly. An assistant placed a finger in the pre-separated "vagina" and pushed it against the mass which was now considerably reduced. Neither the cervix nor external os could even now be identified. An artery clamp was inserted into the fundus and passed through the internal os and into the apparently dilated cervix. The clamp was pressed against the finger in the vagina. An artificial cervicovaginal fistula was deliberately made and a previously shaped pyrex tube ($6\frac{1}{2}$ inch) was passed from above through this cervical vaginal fistula and anchored with two silk sutures. A catheter was then passed from above through the opening in the cul-de-sac into the separated vagina. The abdomen was closed in layers.

FOLLOW-UP

The catheter drain was removed in four days, the abdominal skin showed primary healing, and the sutures were removed in seven days. There was some bleeding from the vagina during this time. Eleven days postoperatively the Pyrex tube was removed and the cervicovaginal fistula could now be sounded for about 4 cm.; the cavity above this artificial os apparently did not go beyond the internal os. The pyrex tube was sterilized and reinserted. On the twenty-fifth postoperative day, the pyrex tube was again removed, the cervicovaginal fistula was dilated, and a uterine retention stem pessary was inserted.

Three weeks after the operation she had a profuse period lasting seven days with pre-dysmenorrhea for two days. Three weeks later she again menstruated for four days, being less profuse and associated with co-dysmenorrhea. Since then she has menstruated every twenty-eight days with no dysmenorrhea, periods lasting four to five days, with a moderate flow.

On April 11, 1939, about six months after the operation, she was again taken to the operating room and under anesthesia the stem pessary was removed, the cervicovaginal fistula was found open and permitted a 22 F. dilator to pass with ease, the sound going into the uterus for about three inches. Bimanual examination could not identify a muscular cervix. The thin dome of the vagina seems to make up the cervix. There is complete epithelization of the vagina, permitting the introduction of two fingers. The acneform eruption of the skin has practically disappeared.

On July 18, 1939, she was again examined under anesthesia, and the cervicovaginal fistula and uterus were again explored. The uterine sound passed up for three and one-half inches; Heger dilators could be passed with ease through the cervicovaginal fistula in sizes 11 to 21 F. As the dilators were passed into the uterine cavity, about 4 ounces of pus were obtained, whose culture was reported negative. At no time has she experienced any fever, abdominal pain, nor dysmenorrhea. The pus was probably encapsulated through the former retention of the stem pessary and had no effect on the physiologic function of the uterus. No cervix can be felt as such but merely the dome of the vagina which forms this cervix. The patient has menstruated regularly since then with no after effects.

SUMMARY

1. The fact that the external genitalia and the lower one-third of the vagina were present and normal in the cases of atresia of the upper two-thirds of the vagina, lends clinical proof to the dual origin of the vagina.

2. Whether the atresia of the upper two-thirds of the vagina before puberty is acquired only or both acquired and congenital is still a debatable question. Clinically, most cases seemed to be of the congenital type.

3. The presence of atresia manifests itself by amenorrhea and pain in the lower abdomen after puberty sets in. Our case and those reviewed revealed a dilated lower uterine portion filled with old accumulated blood.

On Sept. 30, 1938, she was taken to the operating room, and under general anesthesia an attempt was made through further dissection of the "vagina" to approach this mass vaginally and to identify the cervix. The line of cleavage through the rectovesical tissue led into and inadvertently ruptured into the free clean cul-de-sac. Pressure from above through the abdomen could not bring this

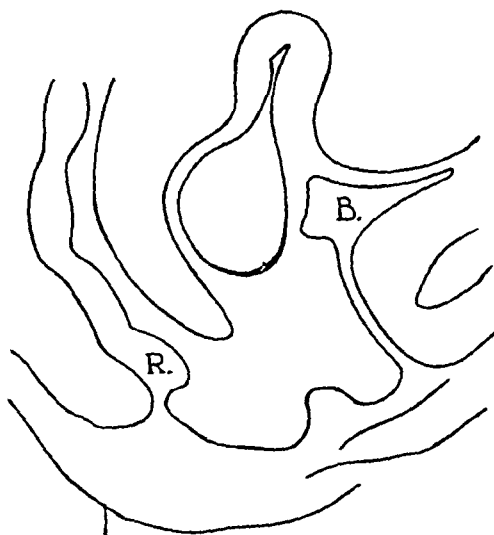


Fig. 1.—Schematic drawing of relations before operation. R, Rectum; B, bladder.

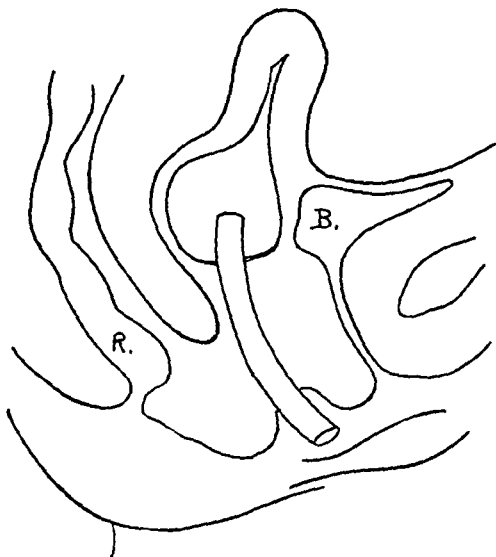


Fig. 2.—After operation.

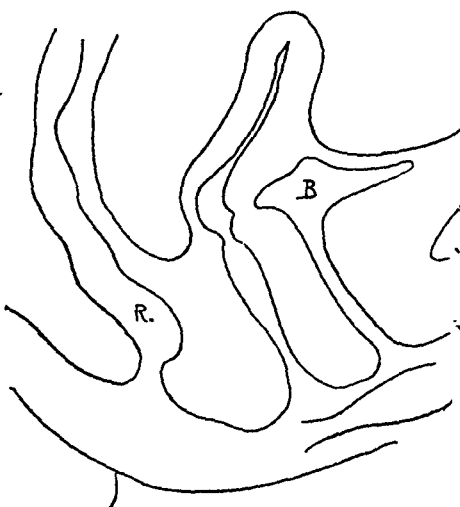


Fig. 3.—End results.

mass down posteriorly to anchor it to the open "fornix" with an attempt to empty this mass through the vagina. The cervix still could neither be identified nor probed.

An abdominal approach was then decided on, which on laparotomy revealed both tubes and ovaries to be normal, the fundus demonstrated no pathology except for a distinct distention of its lower third, especially posteriorly, to about the size of an orange. The cervix as such could not be felt. The bladder was

INTRALIGAMENTOUS GRANULOSA CELL TUMOR

ALEX B. RAGINS, M.S., M.D., AND LEONARD FRANKEL, M.D.
CHICAGO, ILL.

(From the Department of Pathology, Cook County Hospital)

IN AN extensive survey of the literature we have been unable to find any reported case of a granulosa cell tumor of the broad ligament.

R. R., a 37-year-old negress, was admitted to the Cook County Hospital on March 30, 1938, complaining of a progressively enlarging abdomen, associated with stabbing pain in the right lower quadrant, over a period of two months. This pain was more marked when the patient stood erect, and subsided upon reclining. The enlargement was first noted about one year before admission. Except for a period of amenorrhea in March and April of 1937, when the patient first noticed this tumor, she menstruated regularly every twenty-eight days.

During the last year the patient had gained 8 pounds in weight and had become somewhat nauseated and slightly dyspneic on exertion.

The patient was a gravida v, para v. All of the children are living and well, the oldest being 20 years of age and the youngest 12 years of age. Since the age of 12, the patient had been menstruating regularly every twenty-eight days, the menstrual flow being relatively light and of four days' duration. In the past year the menstrual flow was of nine days' duration, with a heavy flow and many blood clots. The period prior to the last one was of seventeen days' duration and was associated with the passage of many blood clots.

The physical examination revealed a well-developed, well-nourished, colored female, about 37 years of age, lying quietly in bed, not acutely ill, and in no apparent pain. The temperature was 98.2° F., respiration 20, pulse rate 96. Blood pressure 120/70. The breasts were atrophic. The heart showed a systolic murmur at the apex. The apex beat was forceful and distinctly visible in the fifth intercostal space in the midclavicular line. A distinct loud second sound was heard over the aortic area. The lungs were essentially negative.

The abdomen showed an eversion of the umbilicus, and a mass arising from the right side of the pelvis, to the right costal margin and above the umbilicus in the midline. It felt smooth and firm and was freely movable. It was not tender on pressure, and definite dullness was elicited on percussion over the mass. Fluid in the abdominal cavity was not made out.

Pelvic examination revealed a normal introitus and the vagina admitted two fingers with ease. The cervix pointed anteriorly and was lacerated and freely movable. The uterus, normal in size, showed a 1 degree retroposition and was displaced to the left. The right adnexal area was the site of a tumor which, on bimanual examination, extended to the right costal arch. The left adnexa were thought to be normal. Hemoglobin, 60 per cent; urinalysis, essentially negative; the blood Kahn, negative.

On the basis of the above findings a diagnosis of a right ovarian cyst was made.

On April 1, 1938, the abdomen was opened through a midline incision. A large cystic tumor mass arising in the right broad ligament was exposed. The right ovary was somewhat flattened by the mass. The left ovary was the size of a small lemon and contained multiple follicular cysts.

A supracervical panhysterectomy was done and the abdomen closed in layers in the usual manner.

Except for a diarrhea which lasted a few days, starting on the sixth post-operative day, the patient made an uneventful recovery and was discharged

4. The use of a glass rod through the artificial cervicovaginal fistula protruding to the lower end of the vagina prevented the raw vaginal walls from agglutinating. Epithelization of the vagina was complete from the proliferation of the squamous epithelium in the lower third of the vagina. Grafting of intestines or skin is apparently unnecessary to form a vaginal lining. Warton¹⁵ has had a similar experience of epithelization of the vagina without grafting although not known to the writer at the time of the operations.

CONCLUSIONS

A girl, who has passed her puberty, who has never menstruated, and who complains of lower abdominal pain, should have a rectoabdominal examination. If this examination reveals a pelvis mass, she is entitled to a vaginal examination, under anesthesia if necessary, to verify its continuity by sounding the vaginocervico-uterine canal before a laparotomy is performed. If the pathology is known before, re-operation for a recurrence of symptoms will be unnecessary, and if the vaginal atresia is first dissected and the operation planned, more conservative surgery will be possible. This patient was left with a uterus, the manifestation of menstruation was established and motherhood was made possible.

Also, extensive operations for an artificial vagina are unnecessary if we let the epithelium from the lower end of the vagina proliferate, thus giving the vagina a normal covering rather than a dry skin or a secreting mucosa.

I wish to extend my thanks to Drs. Walter Kerby and Robert Eckert for their helpful assistance in this case and to Dr. Robert Talisman for his illustrations.

REFERENCES

- (1) *Frazer, J. Ernest*: Manual of Embryology, Baltimore, 1932, William Wood & Co.
- (2) *Jordan, E. Harvey*: Textbook of Embryology, New York, 1937, Appleton-Century Co.
- (3) *Lewis, Dean*: Practice of Surgery 10: Chapt. 2, pp. 8 and 43.
- (4) *Meyer, Robert*: Zentralbl. f. Gynäk. 62: 1810, 1938.
- (5) *King, E. James*: AM. J. OBST. & GYNEC. 3: 290 and 320, 1922.
- (6) *Gemmell, A. Arthur*: Lancet 2: 1061, 1926.
- (7) *Brown, R. Christie*: J. Obst. & Gynec. Brit. Emp. 37: 233, 1930.
- (8) *Bernstein, Pineus, and Walter, S.*: AM. J. OBST. & GYNEC. 37: 126, 1939.
- (9) *Jackson, E. Reginald*: Am. J. Surg. 4: 43, 1928.
- (10) *Mayer, Elek*: Zentralbl. f. Gynäk. 55: 1149, 1931.
- (11) *Gillespie, James, and Davison, Hugh*: Illinois M. J. 73: 491, 1938.
- (12) *Baer, L. Joseph*: AM. J. OBST. & GYNEC. 36: 518, 1938.
- (13) *Gemmell, Arthur*: See reference 6.
- (14) *Fothergill, W. E.*: J. Obst. & Gynaec. Brit. Emp. 32: 336, 1925.
- (15) *Wharton, R. Lawrence*: Ann. Surg. 107: 842, 1938.

Brandstrup, E., and Sindbjerg-Hansen, V.: On Employment of p-Aminobenzol-sulfonamid in Infections of the Urinary Tract During the Puerperium, Acta obstet. et gynec. Scandinav. 19: 195, 1939.

p-Aminobenzolsulfonamid (streptamid) was employed by the authors in infections of the urinary tract in 120 puerperal patients and given in doses of 60 cg. three times daily. On comparison with 439 other patients with pyelitis, streptamid was found to be considerably superior to other medications.

Streptamid given for four days made the urine microscopically bacteria-free in 73 per cent of the cases. Some of the remaining 27 per cent were given additional treatment for four days, which raised the total percentage of recovery to 88 per cent. Treatment with other medication resulted in a microscopically bacteria-free urine in only 51 per cent.

Streptamid therapy is short, inexpensive and convenient; and it requires no restriction of the diet or daily intake of water.

No dangerous by-effects were noted from this treatment. But since a few instances of disturbances have been reported in the literature, with a dosage similar to the one employed by the authors it is advisable to watch the patients closely during the treatment.

the threads. Many of the nuclei contained distinct nucleoli (Fig. 3). Mitotic figures were infrequent and in most instances absent. The cords of cells showed irregular trabeculations which were slightly to moderately separated by dense edematous connective tissue strands.

The tumor extended up to and involved the muscularis of the Fallopian tube which was incorporated with the capsule of the tumor (Fig. 4). In places the capsule adjacent to the wall of the Fallopian tube contained groups of tumor cells



Fig. 2.—Low power magnification $\times 72$. Hemalum and eosin stain, showing thin and thick cords of epithelial-like granulosa cells.

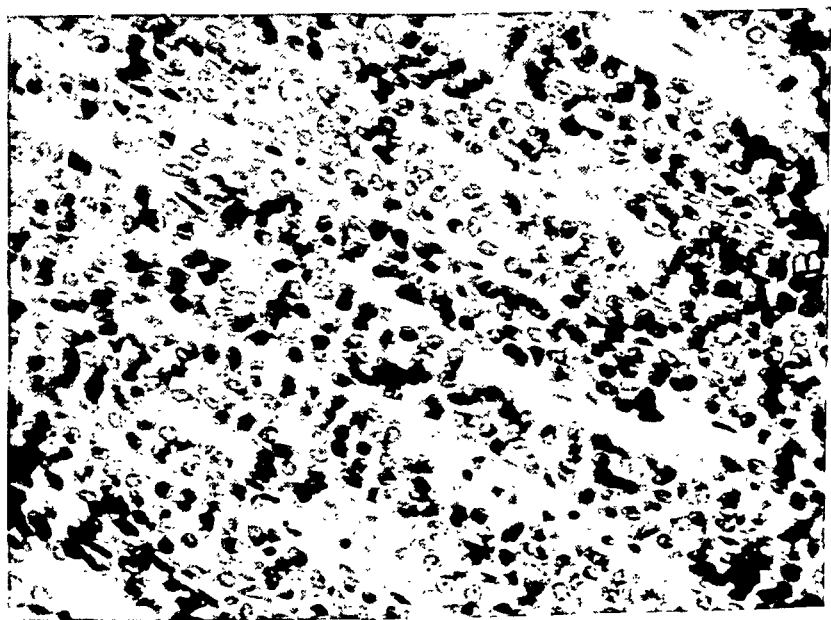


Fig. 3.—High power magnification $\times 300$, showing round and oval-shaped nuclei with fine chromatin granules and distinct nucleoli.

seventeen days after her operation and started on a course of x-ray treatments, as a prophylactic measure against possible recurrence.

PATHOLOGIC REPORT

The specimen consisted of a uterus amputated above the cervix, both Fallopian tubes, both ovaries, and a large intraligamentous mass. The uterus measured 5 by 6 by 3 cm. The wall was 2 cm. thick. The endometrium was 2 mm. thick and purple gray in color. The fimbriated ends of the Fallopian tubes were patent, the walls thin, and the mucosa pale purple gray. The right Fallopian tube was stretched over and formed part of the upper border of a previously opened cystic mass located in the right broad ligament. The mass (Fig. 1) measured 18 by 15 cm. The external surface was a light pinkish gray to yellowish gray in color and slightly nodular. The surface was traversed by numerous blood ves-



Fig. 1.—External surface of intraligamentous tumor, showing the fimbriated end of the Fallopian tube (A) and the right ovary and suspensory ligament (B).

sels. The wall was up to 4 cm. in thickness. The inner aspect was purplish gray to dark gray in color and in some places was smooth, while in others it was covered by a necrotic membrane. The left ovary measured 8 by 4 by 1 cm. and contained several cysts, the largest being 2.5 cm. in its greatest dimension and filled with a clear fluid. The right ovary measured 4 by 1.5 by 2.5 cm. and, on sectioning, contained a corpus luteum of 1.5 cm. in diameter and several small cysts filled with a clear fluid.

Microscopic sections were made from different areas of the tumor mass and stained with hemalum eosin, Mallory phosphotungstic acid hematoxylin, azo carmine, Gömöri reticulum, Weigert elastica, sudan III, and van Gieson stains. Microscopic study of these sections from different areas of the tumor revealed thin and thick cords of epithelial-like cells (Fig. 2) with indistinct cytoplasmic membranes and round to oval shaped nuclei. The chromatin was distributed in the form of fine chromatin threads with fine chromatin granules deposited on

necrotic, connective tissue, infiltrated by many histiocytes containing golden brown pigment granules. The tumor was moderately vascular and contained numerous thin-walled capillaries in the connective tissue bands.

Sudan III stain revealed an occasional tumor cell to contain small sudanophilic droplets in a rather vacuolated cytoplasm. This was particularly noted in single cells which seemed to lie free or border the cords of tumor cells (Fig. 6).



Fig. 6.—Sudan III, magnification $\times 300$, showing small darker staining sudanophilic droplets in the cytoplasm of the tumor cells, lying in the free spaces of the tumor and adjacent to the cords of tumor cell (a).

In addition small amounts of sudanophilic droplets were seen in the connective tissue cells. Gömöri stain revealed a large number of reticulum fibrils in the separating strands of connective tissue which, in places, sent fine, delicate branches into the tumor mass, isolating single cells and small groups of tumor cells.

With the above microscopic findings as a basis, we were led to a diagnosis of an intraligamentous granulosa cell tumor.

SUMMARY

An intraligamentous tumor in a 37-year-old colored woman is presented which, histologically, reveals trabeculae of epithelial-like cells separated by bands of connective tissue. In addition there are islands in which the tumor appears as small glandlike structures with papillary-like processes into the lumen. This places the tumor in the category of the transitional type or mature trabeculated, mature solid type of granulosa cell tumors. This diagnosis is substantiated by the clinical course presented in this patient, as discussed above. The site of the tumor can be explained by the presence of an aberrant ovary or misplaced mesenchymal rests, having the potentiality of forming granulosa cells.

arranged in small alveolar-like structures (Fig. 4) with papillary-like proliferations into the lumina of some of these glandlike structures. The nuclear structures of the cells composing these glandular-like bodies were identical with the epithelial-like cells in the trabeculae described above (Fig. 5). The inner aspect of the tumor, which was grossly cystic, was composed of edematous, and in places,



Fig. 4.—Low power magnification $\times 72$. Hemalum and eosin stain, showing the extension of the tumor around the Fallopian tube, and group of cells arranged in gland-like structures with papillary proliferations into the lumen.

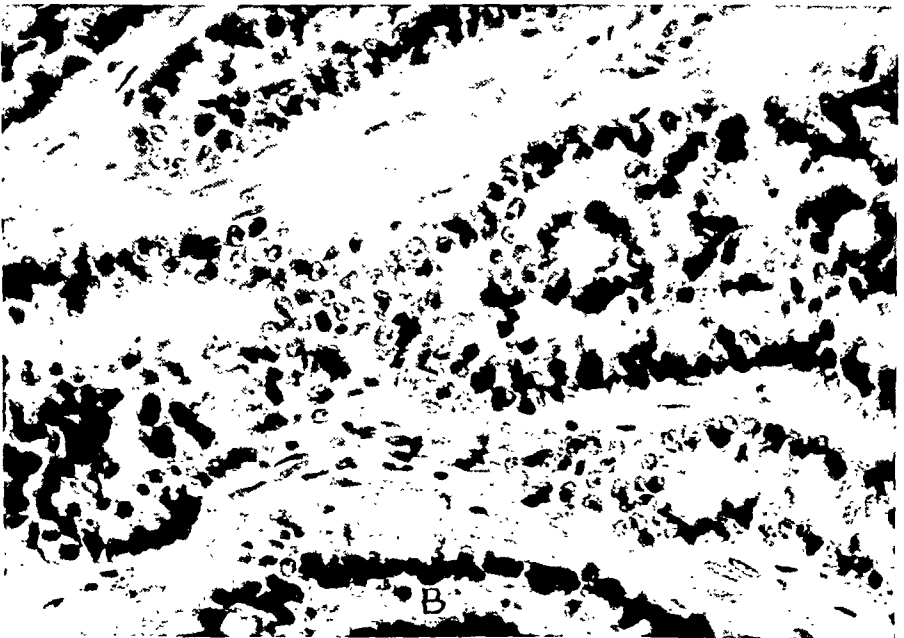


Fig. 5.—Hemalum and eosin stain magnification $\times 300$, showing tumor cells in adenomatous structure similar to tumor cells in the cord.

Colonic and Wangensteen irrigation relieved the distention considerably and flatus was passed freely and abundantly. The nausea ceased. In the morning barium enema x-ray (Dr. W. E. Howes) showed "... Barium filled the rectum, passed through the sigmoid to its proximal third where an obstruction was encountered. An increase in the pressure of the barium column resulted in some overdistention of the rectum. Only a very small amount of the barium passed the point of obstruction, which lay in the left iliac fossa. The barium proximal to the obstruction, appeared to pass into a very narrow channel, perhaps 3 inches or so in length. Palpation of the abdomen was unsatisfactory due to the distention. Patient was rotated to right and left lateral position without any change in the appearance of the barium at the site of the obstruction. . . . The

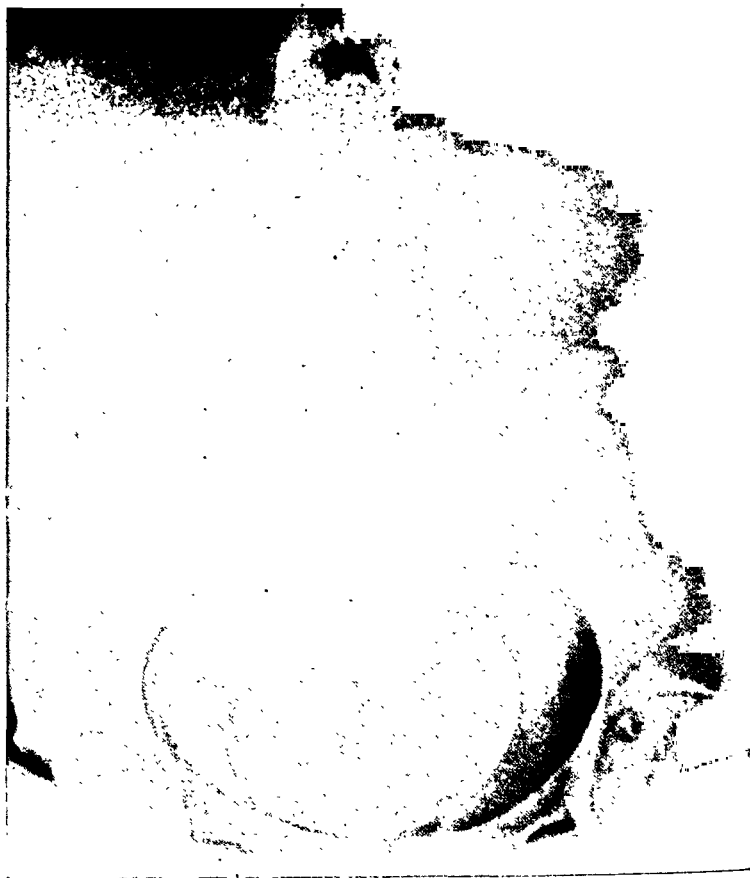


Fig. 1.—X-ray; flat-plate. Marked distention of transverse and descending colon. The distention ends abruptly at the sigmoid. The fetal spine is acutely angulated.

narrow channel proximal to the point of obstruction and the lack of widening of the lumen at the actual point of obstruction suggested an obstruction due to an annular lesion partially obliterating the lumen. . . . The fetal breech was sharply angulated and the fetus thought to be dead" (Fig. 2).

Medical induction, using 4 c.c. of quinine-calcium intravenously, followed at hourly intervals by 3 c.c., 2 c.c., and 1 c.c. of the same solution intramuscularly, was begun at 8:45 that evening. By 2:30 A.M. March 18, labor had started, the cervix was 2 cm. dilated. In order to shorten labor a No. 3 Voorhees bag was introduced at this time. By 9:30 A.M. the bag was expelled and soon thereafter labor ceased. Another cycle of calcium-quinine was given and the membranes were ruptured. The fetal heart was not heard for the first time. She was delivered spontaneously of a live male infant weighing approximately 2,100 Gm.

INTESTINAL OBSTRUCTION DUE TO MALIGNANCY COMPLICATING PREGNANCY

M. G. DERBRUCKE, M.D., BROOKLYN, N. Y.

THE literature contains many reports of isolated cases and collected series of pregnancies complicated by intestinal obstruction and paralytic ileus. The symptoms and objective findings in total occlusion are readily recognizable. This cannot be said of partial occlusion in pregnancy.

The similarity of symptoms found in intestinal obstruction and those commonly associated with pregnancy often confuse the true diagnosis. This is especially true of the partial, recurrent, and intermittent types of ileus. Constipation, an important diagnostic factor in intestinal occlusion is usually present in pregnancy. Distention, the consort of constipation, may appear quite early. Vomiting, a cardinal symptom of ileus, is commonly associated with pregnancy, and pain is often mistaken for the onset of labor.

Although intestinal occlusion associated with pregnancy is not unusual, the occurrence of ileus in pregnancy caused by carcinoma of the bowel and adnexa is quite rare. This infrequency may be ascribed to the fact that malignancy, especially of the bowel tract, is not commonly associated with the active child-bearing age. In the last century only five authenticated reports of such cases have appeared in the medical literature. To these I add two more. One of these occurred on the service of Dr. Charles A. Gordon, at St. Catherine's Hospital, Brooklyn, and the other on my service at the Caledonian Hospital.

CASE 1.—J. G. (No. 461-37), 23 years old, primipara, was seen at home for the first time on the night of March 16, 1937. Two days previously she had returned from a hospital where she had gone one week earlier to seek relief from abdominal distention, constipation, and inability to retain food. She had been followed in the antenatal clinic of this hospital. The findings at this time were "distended tympanitic abdomen. Expression of pain and tenderness over sigmoid colon. Fecal mass palpable. Patient constipated eight days. Low enemas given to break up masses. Patient left hospital to return home, relieved."

There was a history of seven and one-half months' amenorrhea, her last menstrual period being July 15, 1936. Menstruation began at 13, every three weeks, lasting three and one-half days, moderate flow associated with pain. Both parents, 3 brothers, and 3 sisters were living and well. Aside from measles in early childhood, she was never ill until one month prior to her present complaint. At that time she noted she had become extremely constipated, for the relief of which she had entered the hospital. She told me that two days ago the abdominal distention returned and she vomited a clear fluid. The vomitus seemed to be only the liquid she drank, and there was no odor. There was an occasional slight cramp. There was no history of any previous pelvic inflammatory disease or attack of appendicitis. She had not felt any fetal movement in three days.

Physical examination revealed a young, robust woman who did not appear acutely ill. Her tongue was moist and clean. Temperature was 100° F., pulse 88. The abdomen was markedly distended and tympanitic in all except the right lower quadrant, which was occupied by the pregnant uterus. No fetal heart sounds or fetal movements were obtained. Borborygmi was absent. Fetal head seemed forced into the inlet. The cervix and fornices were devoid of any palpable pathology. Rectally, aside from the fetal head, no other masses could be palpated.

That night she was admitted to the Caledonian Hospital. A flat-plate roentgenogram showed ". . . Intestinal loops displaced upward and very markedly distended. . . . The dilated loops extend into left lower abdomen where the distended outline of the gas filled descending colon ends abruptly. No unusual abdominal opacities are demonstrable. . . ." (Fig. 1.)

a disorderly manner in most of the areas. Tube and Ovary: These were both the seat of tumor of the same histologic structure as that observed in the intestines. There were a number of other sections likewise invaded by the adenocarcinoma, but showing no specific normal histologic structure. Their identity was not definitely established.

Diagnosis.—Adenocarcinoma of large intestine with extension to tube, ovary, and pelvic tissues.

Additional laboratory and clinical data: The temperature was normal except for the day of admission when it was 100.4° F. and just prior to her demise when it rose to 109° F. The pulse ranged from 82 to 140 and her respirations were never over 30.

Blood pressure ranged from 144/94 down to 120/80.

The catheterized urine showed 4-plus albumin and sugar, as well as acetone and a few granular casts.

Blood chemistry: Urea 38 mg. per 100 c.c., urea nitrogen 17.7 mg. per 100 c.c., creatinine 2.01 mg. per 100 c.c., chlorides 460 mg. per 100 c.c.

Obviously the annular carcinoma of the bowel antedated the pregnancy. When the uterus and adnexa became abdominal organs, they soon came to lie in direct apposition with the cancerous sigmoid and descending colon. Peritoneal irritation and reaction soon took place and a firm union was formed. From this point both the occlusion and the extension of the growth advanced rapidly.

CASE: 2.—R. McG, white, 36 years, gravida iii, para ii, and now six months pregnant, was admitted to the service of Dr. Charles A. Gordon, St. Catherine's Hospital, Jan. 2, 1937.

There was a history of vomiting, abdominal distention and constipation of one week's duration. Her present illness began suddenly on Dec. 27, 1936, when abdominal distention appeared. Shortly thereafter vomiting, about twice daily, set in and recurred up to the day of admission. The vomitus was green and foul smelling. Constipation, requiring enemas, appeared about four days before admission. The last few enemas were ineffectual. The distention gradually increased.

Other than an appendectomy her past history was entirely negative.

Examination revealed an actually ill gravida with pinched facies, dry tongue, temperature 99.3° F., pulse 112, blood pressure 162/94. Urine showed 4-plus acetone; blood count was essentially normal; blood chlorides, 495. The abdomen was markedly distended. The uterus was felt at the umbilicus; fetal heart rate 144 in the left lower quadrant.

X-ray of abdomen revealed a fetus, six months in size. There was marked gaseous accumulation limited to the small intestines.

Despite enemas, gastric lavage and intravenous glucose therapy, the vomiting and obstipation continued. Surgical consultation (Dr. John Scannell) confirmed the diagnosis of intestinal obstruction.

At operation on Jan. 4, 1937, the abdominal cavity was found to contain a large amount of sanguineous fluid. The omentum was thick, hard and studded with nodules. The small intestines were flaming red and quite distended. A large indurated mass was felt in the sigmoid, evidently the cause of the obstruction. The fluid was evacuated, a biopsy of the omentum obtained, and a cecostomy performed.

Twenty-four hours after the operation the patient went into labor and spontaneously delivered a live 3 pound 2 ounce premature infant, who died in twenty-four hours. The patient rallied and was discharged on the sixtieth postoperative day. The cecostomy was functioning well. At home, however, her condition became worse and she died two months later, from cachexia and terminal bronchopneumonia.

The postoperative diagnosis was: (1) Pregnancy six months, (2) intestinal obstruction, and (3) carcinoma of the sigmoid with omental metastases.

The pathologist's report of the biopsy was metastatic adenocarcinoma of the omentum.

Because of the paucity of instances of malignant neoplasm causing ileus in pregnancy, the recorded cases are herein abstracted.

The site occupied by the uterus was immediately filled with distended bowel. Within a short while her tongue became dry, distention increased, and pain set in. Her general condition was aggravated. With the aid of the Wangenstein irrigation and hypertonic intravenous glucose therapy she improved. The distention was soft throughout except in the left lower quadrant where a hard, solid tender mass was now easily felt. Flatus was passed freely and the distention was considerably reduced. Under gas-oxygen-ether anesthesia, a laparotomy was performed. There was free straw-colored fluid in the peritoneal cavity. The transverse and descending colon was distended but not so large as to offer any trouble with the operative procedure. In the left lower quadrant, matted in a mass the size of a fist, were the lower portion of the descending colon, upper portion of the sigmoid, the left tube, ovary, round ligament and the cornu of the uterus.



Fig. 2.—X-ray; barium enema. The rectum and lower portion of the sigmoid are distended with barium, which can be seen trickling through the narrowed lumen into the descending colon. The fetal spine is sharply angulated.

The mass was readily mobilized and exteriorated. The abdomen was closed. The patient's condition was poor although she responded to intravenous glucose therapy and Wangenstein irrigation. Eight hours later she died.

A complete autopsy was unobtainable but the exteriorated mass was removed immediately post mortem. The pathologist's (Dr. W. W. Hala) report: "The abdominal fluid: Direct smear showed innumerable leucocytes, mostly lymphocytic, an occasional red cell. No neoplastic cells were found."

The Tumor Mass (Gross).—Specimen was resected portion of large gut about 4 inches in length. It was slightly bent on itself. The lumen was almost entirely obliterated by a tumor which not only encircled the gut but had thickened its wall eccentrically by invasion through the submucous, muscular, and serous coats.

Histology.—Section of wall showing presence of a tumor which originated in the mucosa, infiltrated beneath and through the underlying coats, including the serosa. The tumor was adenomatous in structure and retained the architecture albeit in

was a moderate amount of vaginal bleeding. The cervix admitted one finger. The diagnosis was general peritonitis and was possibly due to abortion. She died within twenty-four hours. At autopsy a serofibrinous peritonitis was disclosed, as well as an annular adenocarcinoma of the terminal portion of the ileum with torsion of the ileocecal valve. The uterus showed signs of a recent abortion.

DISCUSSION

While it is reasonably simple to diagnose complete intestinal occlusion in the presence of the classical syndrome of cyclic pain, vomiting, constipation, absence of passage of flatus and distention, it is disconcertingly difficult to state with like assurance that occlusion exists when only one or two of the above symptoms are present.

This latter is definitely more difficult in the presence of a pregnancy. In none of the recorded cases are the early symptom-complaints similar (Table I). Only about one-half of the number, 57 per cent, had any vomiting of sufficient frequency to give it any attention, and in only one case was it severe. Two-thirds of the patients presented constipation as a definite complaint and in only one-half of these was it profound. Only one case had severe cyclic pains as an early sign. Five of the 7 patients had some distention worthy of note, while only one of the 7 did not pass flatus.

It was not until occlusion became complete in 4 of the 7 patients that the diagnosis of intestinal occlusion was made. In two the obstruction was complete before delivery. In the other 5, obstruction became complete after emptying the uterus. In all of these, the empty uterus hastened the occlusion either by direct traction or compression.

The records of 6 are complete. Three of the 6 mothers died before leaving the hospital, and one soon after (66 per cent). There is no record of the duration of life in the others. Two of the infants survived (28 per cent).

A definite lesson can be learned from a review of these cases.

1. The existence of partial or intermittent intestinal occlusion should be strongly considered whenever the symptoms commonly associated with normal pregnancy become exaggerated.
2. Drastic purging is dangerous in cases of prolonged constipation.
3. The diagnosis of occlusion due to neoplasm of the bowel, especially in the partially obstructed cases, can be readily ascertained by roentgenogram.
4. Malignancy apparently has little effect on the pregnancy.

TABLE I. SYMPTOM-COMPLAINTS

AUTHOR	VOMITING		PAIN		CONSTIPATION		DISTENTION		ABSENCE OF FLATUS		PALPABLE TUMOR
	EARLY	LATE	EARLY	LATE	EARLY	LATE	EARLY	LATE	EARLY	LATE	
Maygrier	+	++		++	+++		+	+			+
Lotheisen		+			++++		+				+
Fairbairn	++++										0
Le Gac		+		++		++	+++	++++		++	0
Micale	+	++	+	++	+	++		++	+	++	0
Gordon	+	++			++	++	++++				0
DerBrucke		++		++	++		+	++			0

5. Recognized in the early months, the pregnancy should be disregarded and the neoplasm treated as under all other conditions. Recognized after viability, the fetus should be delivered from below and laparotomy performed for the correction of the obstruction immediately thereafter.

It is fortunate indeed that these instances are rare.

I wish to take this opportunity to thank Dr. Charles A. Gordon for his interest and the privilege to include his case.

SUMMARY OF RECORDED CASES

1. C. Maygrier¹ in February, 1879, reported the first case to the Anatomical Society of Paris. She was a 41-year-old decipara about four months pregnant. With each of her last three or four pregnancies she would become markedly constipated. By the end of the fourth month this would be spontaneously relieved. This time in addition to the constipation, rectal tenesmus, loss of weight, and strength appeared. One week before admission to the hospital she took a powerful purgative. This was followed by severe colic and the sudden passage of a very large amount of fecal matter through the vagina. The vulva and vagina were covered with feces, inflamed, and painful. The cervix was soft, closed, immobile and pushed against the symphysis by a large mass thought to be a fibroid in the cul-de-sac. Immediately behind the cervix was a transverse, indurated, fistulous opening into the rectum. Feces passed only by way of the vagina. One month later, bile stained vomiting began and distention, rectal tenesmus, and crises of colicky pain appeared. Diagnosis of partial obstruction was made. Labor was induced by means of holding a finger in the cervix. Immediately after the delivery the obstruction became complete, and the patient died. At autopsy both ovaries were enlarged, cystic, and adherent. About 9 cm. above the anus, on the posterior wall of the rectum and involving the vagina, was a scirrhus carcinoma. Closing the fistulous opening in the vagina was the posterior wall of the cervix, causing complete obstruction after the delivery. Microscopic examination showed adenocarcinoma of the ovaries with secondary involvement of the rectum and liver metastasis.

2. Lotheisen² reported the second case in 1894 in the Wiener Klinische Wochenschrift. She was a 44-year-old gravida, with a two-year-old history of obstipation. On admission there was a history of no bowel movement for three weeks. A tumor the size of a fist was felt in the region of the sigmoid. Enemas and laxatives only produced the passage of flatus. Bile-tinged vomiting set in about two weeks later. At operation the left ovary, which was involved in a twisted tumor mass, was removed. The right ovary, which was cystic, was also removed. The colon was released and the bowels moved immediately after the operation. Three weeks later she aborted a five months' fetus. The left ovary was the seat of a carcinoma in association with a dermoid cyst. The right ovary contained the corpus luteum.

3. In 1927, John S. Fairbairn,³ in an article on "Acute Abdominal Emergencies Complicating Pregnancy and Puerperium" mentions a case of persistent vomiting for which no other cause than her pregnancy could be found. Shortly after termination of the 7½ months' pregnancy, an urgent operation was performed for obstruction from a carcinoma of the colon, that became obvious very soon after the uterus was emptied. No further data are reported.

4. In 1935 LeGac⁴ treated a 23-year-old primipara who had been delivered two weeks earlier and who now showed evidence of intestinal obstruction. Throughout her pregnancy she was observed by several obstetricians who were always puzzled by the abnormal volume of her abdomen. The abdomen after the delivery retained its unusual size. At this time she complained of pain, marked distention, constipation and no passage of flatus. Enemas gave prompt relief, but all these symptoms recurred six days later with greater intensity. At operation it was necessary to puncture the bowel and evacuate its liquid contents. An enormous tumor of the right ovary to which the small intestine and the sigmoid were attached was disclosed.

The tumor was an atypical "germinative epithelioma" of the ovary. The patient recovered.

5. Guido Micale⁵ in 1936 reported the case of a 38-year-old terzipara admitted to the hospital unconscious. There was a history of fourteen days' amenorrhea. Five days earlier she was seized with severe, diffuse abdominal pains associated with vomiting and absence of any bowel movement or passage of any flatus. This was promptly relieved. The present attack was identical to the first but without regression of symptoms. Examination revealed a rigid, tympanitic abdomen. There

was in active premature labor and was delivered of a four pound, nine ounce male child which cried spontaneously and was obviously more mature than the duration of the amenorrhea of the mother.

The pregnancy was uneventful without any signs of toxemia and the labor normal with delivery under cyclopropane anesthesia.

The puerperium was uneventful until September 20 when the patient complained of pain in the right upper arm and shoulder. The pain was intensified upon lifting the arm above the horizontal plane. There was definite weakness of the flexors of the forearm and hand. On September 25 the pain was decreased except on elevation of the arm, and for the first time slight winging of the scapula on the right side was noted. On September 30 the scapula winging was definitely worse, the pain lessened, and all motions free except elevation of the arm above the horizontal.

Search for the cause of the disability was begun and nothing was found except an impacted lower left third molar which was removed. The patient was seen by an orthopedist who advised support of the shoulder by cast; this was refused by the patient. Palliative measures of diet high in vitamin B and rest of the right arm were carried out. The general health of the patient was good, and the baby did well. On Dec. 12, 1938, the patient had a normal period and then amenorrhea. She was admitted to the University Hospital on April 17, 1939.

Following the onset of the second pregnancy, the patient noted soreness and tenderness in the calf muscles of the leg, and numbness in the legs and feet. She also noted some difficulty in keeping her feet warm. There was slight morning nausea and vomiting but it was not severe. Severe headaches, frontal and occipital in character, occurred frequently. Pelvic examination showed an enlarged pregnant uterus in third degree retroversion and flexion. There was a paralysis of the right serratus anterior with inability to raise shoulder above an angle of 90°. The motor power of the legs was somewhat decreased. There was marked pain to pressure over the gastrocnemius group of muscles. Pain and touch reaction were increased over both lower extremities. Reflexes, coordination, and gait were normal.

Laboratory: Spinal fluid: Initial pressure 3 mm. Hg and rose to 13 cm. on compression of jugulars. The fluid was clear; cell count 5; protein 7 mg. per cent; Kline negative; colloidal gold curve 1100000000 and sugar 68 mg. per cent.

Blood: Serum calcium was 10.5 mg. per cent and the serum phosphorus 5.5 mg. per cent. The hemoglobin was 11.5 Gm.; the red cell count 4,480,000; the white cell count 8,000 with a normal differential.

The patient was given 15 mg. of thiamin chloride daily; 40 drops of oleum percomorphum daily; 5 c.c. of liver extract every other day; 18 gr. of ferrous sulfate daily; and a high vitamin, high carbohydrate diet.

In spite of therapy there was no improvement and a diagnosis of a low grade toxic neuronitis of pregnancy was made. After intradepartmental consultation, a vaginal hysterotomy was done on May 9, 1939.

The patient made an uneventful convalescence and within one week of the termination of pregnancy there was noted an improvement in the patient's general physical condition with lessening of leg symptoms and headache.

She was dismissed from the hospital on the fourteenth day greatly improved.

CASE 3.—Courtesy Dr. W. H. Taylor. The patient, a white female, aged 22 years, had had two previous pregnancies. The first was normal, full term, with a normal delivery on Dec. 3, 1936, and followed by a normal puerperium. The second pregnancy ended in a spontaneous abortion in the second month of gestation, on Aug. 28, 1937. She had a normal period beginning Oct. 28, 1938, and after a normal pregnancy was delivered on July 28, 1939, under nitrous oxide and ether anesthesia. The baby weighed 7 pounds and 12 ounces and was normal. On the fourth post-partum day she complained of some pain in the region of the right scapula, but no particular attention was paid to it.

She was seen on Sept. 9, 1939, with a well-established paralysis of the right serratus anterior muscle. She was advised to use local heat and muscle rest with massage. On Oct. 19, 1939, there had been some improvement although winging of the scapula still occurred. The patient's condition has not improved much at the present time.

REFERENCES

- (1) *Maygrier, Ch.*: Bull. d. Soc. Anat. de Paris, p. 98, 1879. (2) *Lotheisen*: Wien. klin. Wchnschr. p. 911, 1894. (3) *Fairbairn, J. S.*: Brit. M. J. 1: 456, 1927. (4) *LeGac, P.*: Bull. et mém. soc. d. med. de Paris 139: 534, 1935. (5) *Micale, G.*: Riv. ital. di ginec. 19: 141, 1936.

901 WASHINGTON AVENUE

ISOLATED PARALYSIS OF THE SERRATUS ANTERIOR MUSCLE DURING THE PUERPERIUM

LEON S. MCGOOGAN, M.D., OMAHA, NEB.

THE occurrence of an isolated paralysis of the serratus magnus muscle following generalized infections, exposure to cold or trauma to the long thoracic nerve is not uncommon. Horwitz and Tocantins⁴ state that over 150 cases have been reported. The paralysis is more common in men than women and is more frequent on the right than on the left side.

A careful review of the literature reveals only three cases of paralysis of the serratus anterior muscle occurring during the puerperium.

Weber⁵ reported the first case in 1880, and in this instance the paralysis was due to puerperal infection. Gowers³ in 1898 reported a case developing four days after delivery, "excited either by the muscular exertion or exposure of the neck to cold during labor." Berkheiser and Shapiro¹ in 1937 report a case in which they believe the patient injured her right shoulder while pulling on the straps during confinement.

Three additional cases are presented.

CASE 1.—F. B. (Immanuel Hospital No. 62725), white female, aged 20 years, married, para 0, gravida i, had had last menses Jan. 6, 1937. Her expected date of delivery was Oct. 13, 1937. Her pregnancy was entirely normal except that on Sept. 15, 1937, she complained of numbness and tingling in the right arm and hand. These symptoms were transient and disappeared after one week of medication with Brewers yeast tablets, six daily.

The patient was admitted in labor October 6, and after a six-hour labor was delivered by low forceps and episiotomy of a female child, weighing 5 pounds 2 ounces. Anesthesia, open drop ether. On the fourth day, Oct. 9, 1937, the patient complained of pain in the region of the right shoulder which was rather severe but relieved by heat and aspirin. Examination revealed no restriction in motion but the pain was increased on elevation of the arm above the horizontal plane. Under local heat and rest the pain subsided and no deformity of the scapula was noted. On the fourteenth day the patient noted that she could not elevate her arm above a horizontal plane to reach things above her shoulder level. Examination showed definite winging of the scapula. Orthopedic consultation was had and an aeroplane plaster splint advised and refused. Heat, massage, and a high vitamin diet were ordered with arm rest by using a sling support. After six months, complete range of motion was restored, although there was a definite residual weakness of the arm as compared to strength prior to delivery.

She delivered a second child Jan. 26, 1939. The last normal period began May 3, 1938, and the pregnancy was normal until Nov. 28, 1938, when numbness and tingling of the right arm reappeared. The patient was given 6 mg. of thiamin chloride daily with improvement of the symptoms. The delivery was spontaneous and the puerperium normal. Throughout the pregnancy and puerperium there was no change in the condition of the right arm and shoulder nor has there been any change during the sixteen months following delivery.

CASE 2.—K. R. (Immanuel Hospital No. 66888.) The patient, a white female, aged 21 years, was admitted on Sept. 17, 1938, the date of the last menses being Feb. 10, 1938, and the date of expected confinement being Dec. 17, 1938. The patient

BILATERAL SIMULTANEOUS TUBAL PREGNANCY

GEORGE BOLLING LEE, M.D., F.A.C.S., AND
EUGENE T. RUSH STONE, M.D., NEW YORK, N. Y.

(From the Department of Gynecology, New York Polyclinic Medical School and Hospital)

BILATERAL simultaneous tubal pregnancies are of sufficiently rare occurrence to justify reporting any verified case. To the accepted list of 78 cases* of bilateral simultaneous tubal pregnancies, we are adding an additional case with microscopic proof.

R. McQ., colored, aged 29 years, married, had had three pregnancies; first five years ago, second two years later, resulting in a spontaneous miscarriage, and was delivered of a normal child six months ago (May 21, 1939, Harlem Hospital, New York City). Menarche occurred at 13, twenty-eight-day cycle, duration six days. Last menstrual period occurred on Sept. 25, 1939. No history of venereal infection. No previous operations.

Patient was first seen in the Gynecological Clinic, Nov. 20, 1939, and gave a history of having spotted toward the end of October for one day, accompanied by pains in the lower abdomen and rectum. For the next few days, the patient passed a dark vaginal discharge. For the past three weeks, that is, since the spotting which occurred at the end of October, the pains had persisted. There was no further vaginal discharge, no morning nausea. The pains, however, were becoming more severe.

Examination revealed a distended but flaccid abdomen, very tender on pressure. Bimanual and rectal examinations disclosed bilateral doughy and resilient adnexal masses and a boggy mass in the cul-de-sac. The uterus was soft and enlarged, regular in shape, anterior in position. There was no vaginal discharge. A diagnosis of ruptured tubal pregnancy was made and the patient was admitted to the Hospital.

Operation was performed Nov. 22, 1939. Upon opening the peritoneum, free blood and clots were found. The right adnexa were delivered into the incision and a ruptured Fallopian tube was found. The right tube and ovary were excised. Upon examining the left adnexa this tube likewise was found to contain an ectopic gestation and the ovary covered with a clot. This tube and ovary were excised. On Nov. 24, 1939, the patient passed a large uterine cast. The patient made an uneventful recovery and was discharged in good condition from the hospital on the thirteenth day.

Pathologic Examination by Dr. A. Sumner Price: "The specimen consists of two large tuboovarian masses.

"A. The right tube measures about 3.5 cm. in diameter for about two-thirds of its length. It is covered with blood clot and is apparently filled with it. The external appearance suggests an ectopic pregnancy. The ovary shows a large corpus luteum, some edema, and blood clot over the surface. When the tube is incised, on one side is found a portion of degenerated embryo about 14 mm. in length. A yolk-like structure can be recognized. The entire chorionic mass is about 3.5 cm. in diameter. The corpus luteum of the ovary measures about 2 cm. in diameter.

"B. The left tube is dilated to about 3 cm. in diameter in the distal third and is apparently filled with blood clot. The ovary attached shows edema and a large corpus luteum. When this tube is incised, it shows a chorionic mass about 3 cm. in diameter which contains a cystic cavity of slightly irregular outline in the central

*Fishback, H. R.: AM. J. OBST. & GYNEC. 37: 1035, 1939; Torpin, R.: Ibid. 39: 345, 1940.

DISCUSSION

In all of these cases and in the three cases reported in the literature, the paralysis was on the right side. The three patients presented were all right handed and the more active shoulder was paralyzed. The predilection for right-sided involvement suggests that perhaps the nerves to an active group of muscles are more susceptible to damage, which occurs either as a result of anatomic peculiarities or from deficiency states.

The first symptom is pain in the shoulder region and in all instances it occurred on the fourth post-partum day. The winging of the scapula was not noted until later, and in the one carefully observed case appeared on the ninth day.

The cause of the isolated paralysis of the serratus magnus in the reported cases has two possible explanations. Horwitz and Tocantins claim that a lateral tilt of the head and the neck puts the nerve on tension, with injury to the nerve as it comes across the chest cage. This tilt might occur during anesthesia as the anesthesiologist frequently tilts the head forcibly to prevent aspiration of regurgitated gastric contents or swallowing of the tongue. Whether this occurred in these cases or not cannot be verified. It would seem that paralysis from this cause might be a more frequent sequel than it seems. Apparently it is very uncommon. The second possible explanation is that the paralysis is a manifestation of an unrecognized vitamin B deficiency or of a recognized deficiency inadequately treated. This latter explanation seems to be most plausible.

In the first case, symptoms of vitamin B deficiency were presented three weeks prior to delivery but they subsided on vitamin B complex therapy. The same symptoms recurred during a subsequent pregnancy but more intensive therapy was used and the paralysis failed to occur.

In the second case no history of vitamin B deficiency was obtainable prior to the onset of the paralysis. A subsequent pregnancy which had its inception three months after the first pregnancy was terminated was complicated by a varied but rather typical symptom syndrome of vitamin B deficiency—in spite of the fact that she had been on a fortified vitamin B diet. Either the amount of vitamin B given was inadequate or there was failure of utilization of the orally administered vitamin.

The treatment consists of muscle rest, preferably in a cast or splint, but if that cannot be done, support and rest in a sling. This should be re-enforced with local heat and massage. The diet must be high in vitamin B content or supplemented with an adequate amount of thiamin chloride intramuscularly.

REFERENCES

- (1) *Berkheiser, E. J., and Shapiro, F.*: J. A. M. A. 108: 1790, 1937. (2) *Bunts, F. E.*: Internat. J. Surg. 17: 320, 1904. (3) *Gowers, W. R.*: Diseases of the Nervous System, ed. 2, Vol. 1, Philadelphia, 1898, Blakiston, Son & Co., p. 82. (4) *Horwitz, M. Thomas, and Tocantins, L. M.*: J. Bone & Joint Surg. 20: 720, 1938. (5) *Weber*: Deutsche med. Wchnschr. 277, 1880; Quoted by Tournay, A., and Kraus, M. J. Neurol. & Psychopath. 5: 115, 1924.

considerable hemorrhage over the surface. In the interior is found blood clot, chorionic villi, and an abundance of syncytial and trophoblastic cells (Fig. 1). At one point there is considerable hemorrhage and leucocytic reaction in the wall, which suggests rupture at this point. There is also found a portion of embryonic tissue in which primitive neural and enteric elements can be recognized which are forming from a mesenchymal mass.

"Microscopic examination of the mass marked 'B' shows a large corpus luteum of the ovary, with some hemorrhage over the surface. The tube on this side is dilated and contains blood clot, an abundance of chorionic villi, and decidua of pregnancy (Fig. 2). The chorionic villi are of the same general structure and of about the same degree of maturity as those found in the first mass.

"Diagnosis: Bilateral ectopic tubal pregnancy and bilateral corpus luteum of ovary."

EXTRAOVARIAN GRANULOSA CELL TUMOR

CUTHBERT POWELL, M.D., F.A.C.S., AND WILLIAM C. BLACK, M.D.,
DENVER, COLO.

(From the Department of Obstetrics and Gynecology, and the Department of Pathology, University of Colorado School of Medicine and Hospitals)

WITH very few exceptions, granulosa cell tumors are found in the ovary. Voigt¹ has reported a retroperitoneal granulosa cell tumor in a woman past the menopause, in which the histologic structure was characteristic, and from which a biologically active extract was obtained. Compton² reports a granulosa cell tumor of the left ovary, with occurrence sixteen years later, in the same patient, of another granulosa cell tumor located in the right vesicouterine fold. It was in no way connected with the right ovary.

A report of a third extraovarian granulosa cell tumor by Ragins and Frankel³ appears on p. 302, this issue.

The following is a report of an encapsulated, partially cystic tumor situated in the left broad ligament. We believe that there is sufficient evidence to prove that this is a granulosa cell tumor, and that the case is of particular interest because of the extraovarian location of the tumor.

CASE HISTORY

Mrs. L. H., a 30-year-old, white married woman was admitted to the Gynecologic Service of the Colorado General Hospital on April 21, 1939.

Menstruation began at the age of ten years. The periods were regular, every thirty days, lasting four days, with little or no pain. At the age of sixteen years she began to have moderate dysmenorrhea. The flow, however, continued normal in amount.

At the age of twenty the patient was married. There soon followed in rapid succession five pregnancies, all of which terminated spontaneously in from three to seven months. There was marked nausea and vomiting throughout all of the pregnancies, and menstruation occurred in normal amounts with but slight irregularity.

The sixth pregnancy continued for eight months, possibly due to bed rest for approximately four months during this time. Three or four times during this pregnancy she menstruated at the time the menses might be expected to occur. This pregnancy terminated at eight months in the birth of a male child which survived.

The patient's husband died after five years, and two years later she married again at the age of twenty-seven. Her seventh pregnancy soon followed and continued for seven months, when she was delivered of a premature female baby which survived.

The eighth pregnancy terminated by spontaneous miscarriage at five months in the Colorado General Hospital in January, 1939. This baby lived for about eighteen

area, measuring about 1.5 cm. in diameter. No embryo is found on this side. The ovary shows a corpus luteum about 1.5 cm. in diameter and is slightly cystic. Separately is a mass of blood clot measuring about 4 by 3 cm.

“Microscopic examination of the mass marked ‘A’ shows a large corpus luteum of the ovary, with numerous immature germinal cells in the cortex. The tube shows

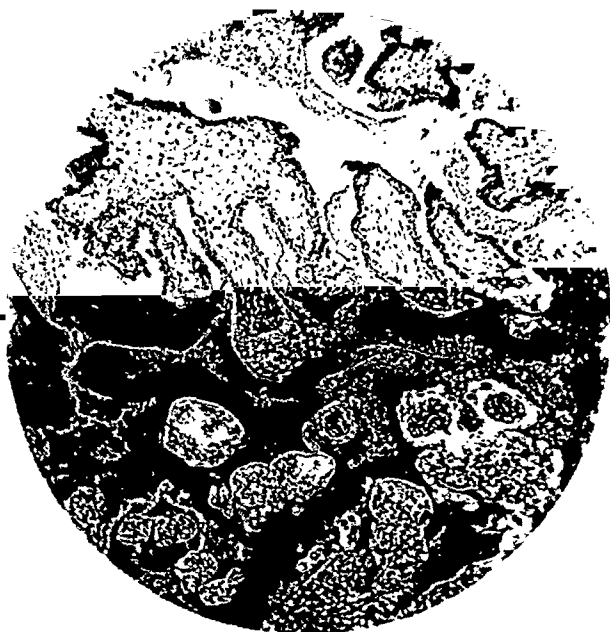


Fig. 1.—Young chorionic villi from “A” (right) tube showing an abundance of trophoblastic cells in the lower half of picture.



Fig. 2.—Young chorionic villi found in tube (left) “B”. There is an abundance of trophoblastic cells at the top of the picture. The chorionic villi are slightly more edematous than in “A”; hemorrhage is more marked, but the villi are of approximately the same age.

Microscopically, the tumor was made up of irregularly shaped fusiform cells with large coarsely reticular nuclei and scanty eosinophilic cytoplasm. These cells were supported by a delicate connective tissue reticulum containing numerous capillary blood and lymphatic vessels. The arrangement of the tumor cells varied some-

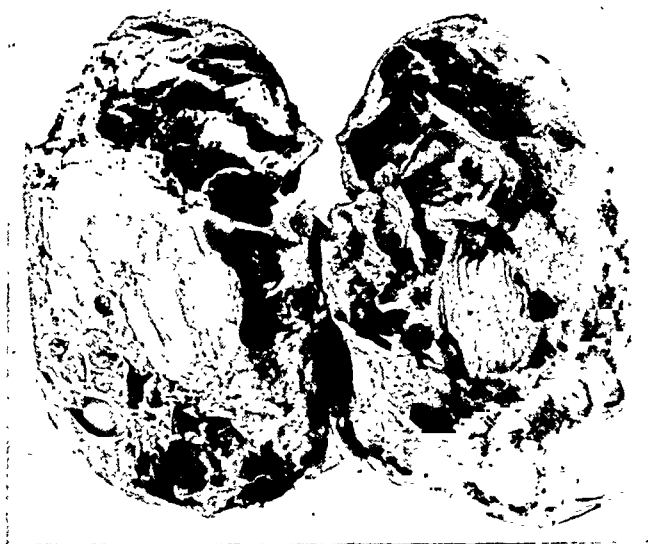


Fig. 1.—Polycystic tumor from the left broad ligament.

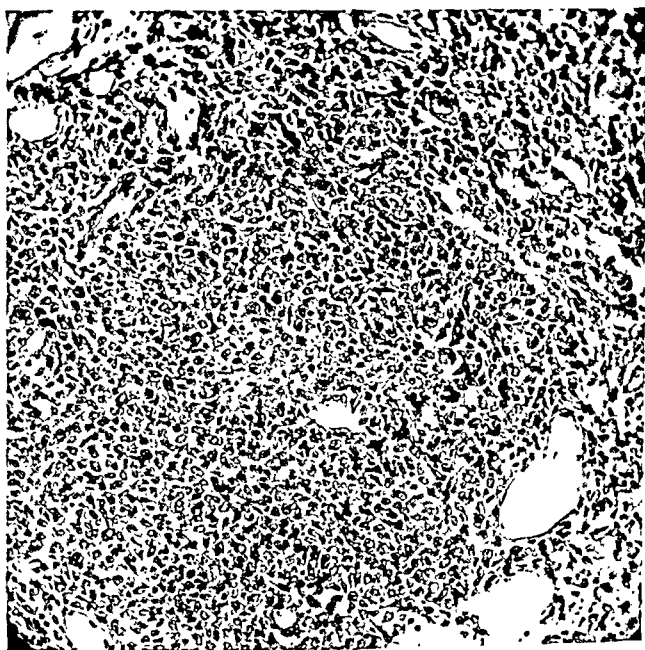


Fig. 2.—Granulosa cell tumor. Partially cystic zone. $\times 140$.

what in different regions, but, in general, the cells lay in small compact whorls and interlacing bundles. This arrangement suggested that of normal ovarian cortical stroma. Throughout the tumor there was alternation of densely cellular zones and loose areolar connective tissue. Fusiform tumor cells extended outward from the denser zones into the areolar tissue along the intercellular fibrils.

hours. This pregnancy was also characterized by normal menstruation at each regular period. In fact, due to the regularity of the periods, the patient was four months' pregnant before realizing her condition.

Following this miscarriage, the patient first became cognizant of a palpable mass in the lower left abdominal quadrant, associated with bearing down pain. She had become increasingly nervous and irritable. Migraine with which she has suffered most of her life became more frequent and severe.

Aside from three attacks of pneumonia during childhood, and a left otitis media which discharged until a few years ago, leaving marked impairment of hearing in this ear, the history other than cited was negative.

On admission examination revealed a well-developed, fairly well-nourished female of apparently her stated age. She did not appear to be acutely ill and was not in pain. Temperature was 99.2° F., pulse 94, blood pressure 118/76. Red blood count and hemoglobin were normal. White blood count was 12,240 with 66 per cent polymorphonuclears. Urine was negative; Wassermann negative.

There was a large, moderately soft, nonfluctuant mass in the left side of the pelvis, not freely movable. It was apparently not connected with the uterus, which was freely movable and appeared normal as did the right adnexa.

A diagnosis of ovarian cyst, probably cystadenoma, was made.

A low midline abdominal incision was made on April 24, 1939, adequately exposing the uterus, tubes, and ovaries, all of which appeared to be normal.

Lying below the left tube, between the folds of the broad ligament, was a mass corresponding in size and consistency to that found on pre-operative examination. An incision was made in the anterior leaf of the left broad ligament and the mass was easily enucleated by finger dissection. There was no pedicle. The incision in the broad ligament was closed, the appendix removed incidentally and abdomen closed in the usual manner.

The specimen removed consisted of an encapsulated spheroidal tumor measuring 10 by 7 by 5 cm. Externally it was grayish red and coarsely nodular, with a row of adipose and fibrous tissue tags along one surface.

Two days later, due to the apparent nature of the tumor, a light curettage was done in order to obtain a specimen of endometrium for study.

For eight days following the operation there was uterine bleeding, usual after removal of granulosa cell tumors. Aside from this the postoperative course was uneventful.

It had not been possible to examine this patient since her discharge from the hospital. However, in a personal communication received on Dec. 14, 1939, approximately eight months after removal of the tumor, she stated that her health was better since her operation, but that she was pregnant and had pain in the left side at times. She had menstruated three times since the operation; on June 3, 5 days; July 3, and August 3, each one day.

In a subsequent communication, Dr. G. L. Robinson of Salida, Colorado, states that he delivered this patient at term on Feb. 20, 1940, of a normal female baby weighing 6 pounds and 9 ounces. The mother reports that the baby is normal, that she is nursing it and that her own health is better than before.

From the above case history it is evident that genital function has been abnormal, but the history is not that of a typical granulosa cell tumor, with which, in the child-bearing period, one would expect a history of amenorrhea or anovulatory menstruation with more or less profuse metrorrhagia at irregular intervals. Because of the atypical history, it is necessary to assume that the tumor, being of the diffuse or sarcomatoid type, produced relatively little estrogenic hormone and that the amount produced was insufficient to inhibit normal follicle maturation and ovulation. The endocrine effect of the tumor, although comparatively slight, may have been sufficient to interfere with the course of the patient's pregnancies.

Pathologic Report.—The tumor was spheroidal, fully encapsulated, and as above stated in size and external appearance. It was composed of pale yellowish gray soft tissue, containing many cysts, varying from 0.1 to 3.0 cm. in diameter. The cysts had a smooth lining and contained clear or slightly turbid watery fluid (Fig. 1).

rhagic zones in the superficial portion. Surface epithelium was not present, evidently having been desquamated together with a portion of the underlying endometrium (Fig. 4).

DISCUSSION

Comparison of this tumor with the one reported by Eastlake⁴ in 1931 shows close similarity in structure. It is noteworthy that Eastlake's patient, a child aged three, developed *pubertas praecox* although the tumor was of the relatively undifferentiated diffuse (sarcomatoid) type.

No biologic assay for estrin content of the patient's urine or blood, nor of the tumor tissue was attempted, because the nature of the tumor was not suspected until after its removal and fixation. In this connection it should be mentioned that in patients in the child-bearing period, biologic assay is of less value than might be expected as the amount of estrin present may vary widely within normal limits (Gustavson and others,⁵ Dworzak and Podleschka⁶).

The extraovarian location of this tumor is an important feature of the case. Extraovarian granulosa cell tumors are rare, only two having been previously reported, but are of great interest from the viewpoint of histogenesis.

In embryonic life the gonads of both sexes develop from the genital fold. In the female it has been long thought that the follicular lining cells are derived from the "germinal" epithelium covering the surface of the genital fold at the ovarian site. The germ cells have been thought also to migrate inward from this epithelial layer.

Fischel's⁷ embryologic studies indicate that this is not true, but that the germ cells originate in the entoderm, and migrate into the mesenchymal zone of the germinal ridge where the surrounding mesenchymal cells differentiate to form primordial follicles. According to Fischel's concept the power of forming an organ (ovary) is originally possessed by the mesenchymal cells in a large area which is gradually restricted to a narrower field, which in turn ultimately becomes the gonad. However, the mesenchymal cells beyond this field retain a potentiality for differentiation, if stimulated to development. Variation in histologic structure in granulosa cell tumors is probably dependent upon the stage of differentiation of the tumor cells toward the adult granulosa cell form, and explains why, in the words of Schiller,⁸ "The tumors when unripe have the character of connective tissue, and when ripe show epithelial structure." Thus undifferentiated but potentially specific granulosa cells may remain in the territory originally occupied by the genital fold. In the adult this zone extends retroperitoneally from the region of the adrenal to the cortex of the ovary. It is in this area that extraovarian granulosa cell tumors may be expected to occur.

Granulosa cell tumors of the ovary are commonly believed to originate from granulosa cell rests, although some authors have found evidence that such tumors may be derived from previously normal follicular lining cells. Butterworth,⁹ on the basis of experimental irradiation of the ovaries of senile mice, found granulosa cell tumors apparently developing from normal follicles following degeneration of the ova. Robinson¹⁰ in 1930, on the basis of four cases reported by him, claimed that the granulosa of the follicles is the genetic source of granulosa cell cancer. In one of his cases he believes that tumor growth from follicular lining can be traced. In this case, however, there were changes in the voice and hair distribution, with hirsutism suggesting masculinization.

Dockerty and MacCarty¹¹ in 1939 reported a case of granulosa cell tumor in which origin from follicular epithelium is considered probable by the authors. Many follicles which appeared otherwise normal presented localized hyperplasia of the granulosa cells with extension to involve surrounding tissue.

While origin from follicular lining cells within the ovary is debatable, such origin in an extraovarian tumor would be unlikely. Origin of the tumor from a granulosa cell rest of mesenchymal derivation seems to be a more reasonable conclusion, and is supported both embryologically and by the sarcomatoid appearance of the tumor cells.

SUMMARY

A case of extraovarian granulosa cell tumor is described. It is believed to be clinically benign. There is evidence that the tumor caused disturbance of genital

The cysts were situated in the denser zones and had no epithelial lining. Tumor cells formed the walls. The cysts might be emptied or filled with faintly eosinophilic granular material (Fig. 2).

In the densely cellular zones some of the centrally located cells were hyperchromatic, with bizarre nuclear forms and occasional mitotic figures. Small groups of cells in such zones had a folliculoid arrangement, but Call-Exner bodies were not seen (Fig. 3).

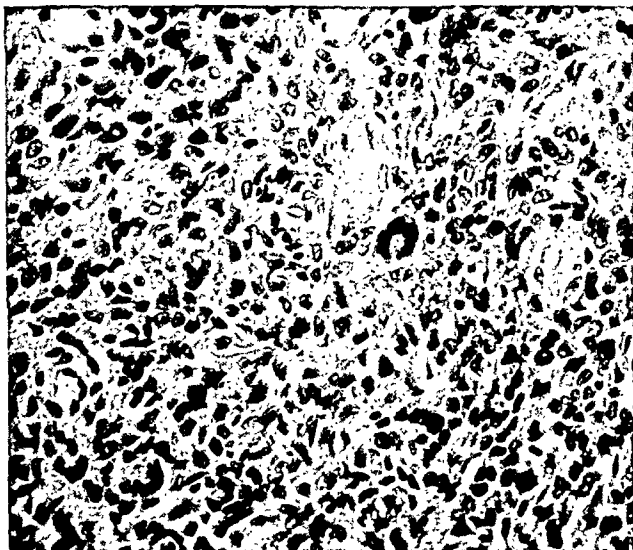


Fig. 3.—Granulosa cell tumor. Solid zone. $\times 200$.

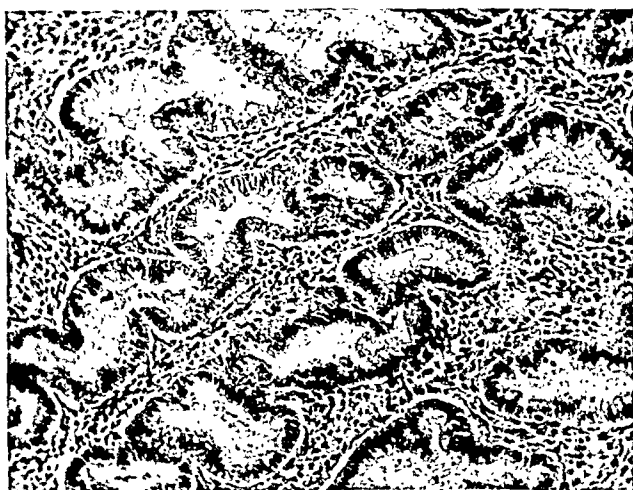


Fig. 4.—Specimen of endometrium showing glandular hyperplasia. $\times 140$.

Small collections of lymphoid cells were present in the tumor, situated in perivascular connective tissue, and scattered leucocytes, chiefly lymphoid, lay between the tumor cells.

Histologic examination of the endometrium revealed closely grouped, moderately tortuous, endometrial glands with tall columnar basophilic epithelium, in some instances infolded. The lumina of the glands contained pink-staining granular precipitate and occasional leucocytes and erythrocytes. The endometrial stroma was made up of small darkly-stained fusiform cells and was edematous, with small hemor-

Unquestionably in the presence of an enlarged friable spleen the most minimal internal trauma, often unrecognized, may cause rupture. Klotz in discussing Kehrer's⁶ case believed the indirect action of force to be analogous to the coup and contracoup injuries sustained in skull fracture. In this manner an abrupt change of position or the sharp contraction of the abdominal musculature and the uterus accompanying bearing down may push the spleen against the left lobe of the liver or the costal margin, causing rupture.

Pathologically two types of rupture are discernible. The most common is the complete tear involving both the parenchyma and capsule. The other type may be called an incomplete rupture and involves the parenchyma alone, causing the formation of a subcapsular hematoma. This type probably accounts for the classic signs and symptoms of early rupture, and only when the capsule is ruptured does intra-abdominal hemorrhage with signs of shock intervene. If the condition is not recognized early, with the institution of proper shock therapy followed by immediate splenectomy, death rapidly ensues.

As far as I could ascertain this is the first case of spontaneous splenic rupture complicating labor reported in the American literature.

In 1925, Stretton⁷ reported a case with recovery that had come to operation diagnosed as ruptured ectopic gestation. Kotschnew and Manenkow² in 1930 reported 14 cases collected from the literature to which they added a fatal case of their own. Bohler⁸ in 1932 added another case. Two cases appeared in the British journals reported by Smith, Morrison and Sladder⁹ in 1933, and by Burnett and McMerrimey¹⁰ in 1935. Since then two other cases have appeared in the German literature, recorded by Sommer¹¹ in 1937 and R. v. Hoch¹² in 1938.

CASE REPORT

Mrs. M. R. (Case 137220), a 34-year-old, white multipara, was admitted to the Obstetrical Service of the Cincinnati General Hospital on Jan. 24, 1940 with a history of slight vaginal bleeding and ruptured membranes.

Her last period occurred June 19, 1939. She was a patient in the prenatal department of this hospital and had been attending the clinic regularly. Her pregnancy progressed normally up until four days before admission when she developed a slight upper respiratory infection. Two days prior to admission the patient noticed slight, painless vaginal bleeding. This continued intermittently until her membranes ruptured spontaneously on the day of admission.

Past History.—Essentially negative except for the usual childhood diseases. She gave no history of malaria or typhoid fever, and did not use alcohol in any form. Catamenia occurred at 14, periods regular every twenty-eight days, lasting from three to four days.

She had been married for the past thirteen years, had had 6 pregnancies including the present; two children living and well, and three children dead (two in the neonatal period, 1 at 6 months, cause unknown).

On admission, temperature was 100.6° F., pulse 80, respirations 20, blood pressure 125/70. Blood Wassermann, Kahn test and urinalysis were negative.

Physical examination revealed only slight evidence of acute upper respiratory infection and heart and lungs were normal. Obstetric measurements were adequate. Uterus was at term, presenting part floating, back on the left, fetal heart rate 134 and regular. Rectal examination revealed a long, soft cervix, 1 finger dilated. Since the patient was not in labor, she was sent to the ward and isolated.

Patient soon became temperature free, congestion of the nose and throat cleared and she was apparently well. A medical induction was attempted three days after admission but without results. On January 29 patient had a severe chill, lasting for twenty minutes, temperature 104° F., pulse rapid but of good quality. Patient offered no subjective complaints of any kind. Red blood count, 2,600,000; white blood count, 13,000; Hb, 10 (Sahli). Examination of the chest revealed a few diffuse rales at the right base. The emergency chest plate revealed no ab-

function with endometrial hyperplasia and repeated abortion or miscarriage. The patient's only normal full-term pregnancy occurred after surgical removal of the tumor. Histogenesis of the tumor is discussed.

REFERENCES

- (1) Voigt, W. W.: AM. J. OBST. & GYNEC. 36: 688, 1938. (2) Compton, B. C.: Ibid. 34: 85, 1937. (3) Ragins, A. B., and Frankel, L.: Ibid. 40: 302, 1939. (4) Eastlake, A. C.: Colorado Med. 28: 404, 1931. (5) Gustavson, Mason, Hays, Wood, and D'Amour: AM. J. OBST. & GYNEC. 35: 115, 1938. (6) Dworsak and Podleschka: Arch. f. Gynäk. 154: 441, 1933. (7) Fischel, A.: Ztschr. d. ges. Anat. 92: 34, 1930. (8) Schiller, W.: J. Obst. & Gynaec. Brit. Emp. 43: 1135, 1936. (9) Butterworth, J. S.: Am. J. Cancer 31: 85, 1937. (10) Robinson, M. R.: Surg. Gynec. Obst. 51: 321, 1930. (11) Dockerty, M. B., and MacCarty, W. C.: AM. J. OBST. & GYNEC. 38: 698, 1939.

SPONTANEOUS RUPTURE OF THE SPLEEN COMPLICATING LABOR

WILLIAM F. SHANNON, A.B., M.D., CINCINNATI, OHIO

(From the Department of Obstetrics, University of Cincinnati, College of Medicine and Cincinnati General Hospital)

TRAUMATIC or spontaneous rupture of the spleen is not an uncommon occurrence in the nonpregnant state. However, rupture of the spleen occurring spontaneously during pregnancy, labor, or the early puerperium is quite unusual, almost rare enough to be called a medical curiosity. Because of this rarity, difficulty in diagnosis, and rapidity of death, most cases are not recognized during life and are discovered only at autopsy.

Etiology.—In more than half of the reported cases of splenic rupture complicating pregnancy, there is a definite history of trauma. In the group classified as spontaneous rupture the etiologic factors are still obscure. Certain factors, however, may be considered. Walton¹ has stated that splenomegaly accompanied almost every case of spontaneous splenic rupture recorded in the literature. Therefore, it seems that from an etiologic standpoint the question revolves around the cause of the accompanying splenomegaly. From the literature 9 cases of spontaneous splenic rupture were collected. Seven of these showed varying degrees of splenomegaly, and in only 1 case (case of Hubbard) was there a definite pathologic reason, malaria.

The question as to whether or not uncomplicated pregnancy might in itself be the cause of physiologic enlargement of the spleen has been entertained by previous writers. Kotschnew and Manenkow² believe that in pregnancy the splenic pulp may proliferate causing enlargement of the organ. De Lee³ states that the spleen increases somewhat in size during pregnancy. Dameshek⁴ points out that the spleen observed after death often gives an erroneous idea of its size, and when it is observed in the human being at operation, the spleen is a much larger organ, varying normally in size from 250 to 350 Gm.

On the other hand Barcroft and Stevens⁵ have shown in the dog and other laboratory animals that the size of the exteriorized spleen varies during pregnancy and that it probably reaches its smallest size a few days before labor. They attribute this shrinkage to the need for supplying blood to meet the increased capacity of the vascular bed caused by dilatation of the uterine vessels.

Serbin¹⁴ in a recent report comments, "Pregnancy does not cause the spleen to undergo any appreciable hypertrophy, any enlargement is due to pre-existing disease." Further he adds, "Splenomegaly is sufficiently rare complicating pregnancy to warrant the addition of all observed cases to the literature."

The effect, therefore, of pregnancy as an etiologic factor of splenomegaly in the human still remains a moot question.

Microscopic Diagnosis.—Acute passive congestion of the lungs, liver, and spleen; focal hemorrhage in the lungs and stomach; toxic hepatosis and nephrosis; recently post-partum uterus.

Microscopic Description: Sections of the spleen showed sinusoids markedly dilated and engorged with erythrocytes and polymorphonuclear leucocytes. In some areas the walls of the sinusoids were disintegrated with the formation of pools in the splenic tissue. Some of these contained pinkish, granular material, probably laked blood, while others contained chiefly erythrocytes. The margins of the break in the splenic capsule showed no cellular reaction.

The lungs presented marked dilatation of the capillaries with erythrocytes and occasionally macrophages. In the sections of the right lower lobe there were focal hemorrhages.

The liver showed marked dilatation of the central veins and sinusoids. In some of the latter there were no recognizable red cells but only a granular fluid like that described in pools in the spleen. The cells of the liver cords were markedly granular with vacuolization of their cytoplasm.

The kidneys showed swelling of the cells of the convoluted tubules as well as pronounced granularity of their cytoplasm.

The uterus presented ulceration of the endometrium with a moderate polymorphonuclear infiltration of the surface. The blood sinuses were large and collapsed. The muscle fibers were hypertrophied.

Sections of the bone marrow revealed no abnormality. The heart, aorta, arteries, suprarenals, pancreas, breast, ovary, and gall bladder appeared normal.

DISCUSSION

In all, 22 cases including the present report, have been recorded in the literature. In addition, 6 cases of rupture of an aneurysm of the splenic artery complicating pregnancy were found (Smith, Wessenberg, Lundwall, Mayer, Remmelt,² and Bohler¹³). All the cases of splenic rupture occurred in white women, and these, with the exception of one, were multiparas. Due to a lack of sufficient information, the exact time in gestation at which this accident occurred was not definitely known in the entire group. Twenty of these cases give some information as to the time of occurrence in pregnancy. Of these, 12 occurred after viability, 7 early in pregnancy, and 1 in the immediate puerperium. Of the cases which happened late in pregnancy 5 occurred during labor, besides the present case (Kotschnew, Simpson, McMerrimey, Sommer and v. Hoch). In the last three cases mentioned, signs referable to subcapsular rupture of the spleen were present days before the actual onset of labor. Ten cases out of 22 came to surgery. Of these 8 recovered after splenectomy. One case (Smith, McMerrimey and Sladder) went on to term after having a splenectomy at three months.

Of the entire series 14 patients died. The cause of death of the majority of these was discovered only at post mortem. The difficulty of diagnosis, especially so in the presence of the gravid uterus, and the rapidity of death following this accident are responsible for the high mortality rate. Early in pregnancy the diagnosis is most often confused with ruptured ectopic gestation, later with premature separation of the placenta and rupture of the uterus. As pregnancy nears term the difficulty is manifoldly increased, and when rupture occurs during labor, as exemplified by this present case report, the diagnosis is almost an impossibility.

SUMMARY

1. A case of spontaneous rupture of the spleen complicating labor is reported. It is believed to be the first case recorded in the American literature.

2. Twenty-one cases of splenic rupture complicating pregnancy, labor, and the puerperium have been collected from the literature.

3. Due to difficulty in diagnosis and rapidity of death, spontaneous splenic rupture complicating labor may be an unrecognized cause, albeit a minor one, of fatal obstetric shock.

normalities. Fluids were forced and the temperature dropped below normal at 8 P.M. The blood pressure at this time was 120/80, pulse 85 and regular.

A few minutes after midnight, Jan. 30, 1940 the patient commenced to have regular uterine contractions. Rectal examination revealed a soft mass presenting, presumably a breech. Fetal heart had not been heard since early afternoon. At 1:40 A.M. the cord prolapsed, but since no pulsation was felt, and the fetal heart had not been heard for several hours, interference was not contemplated. About five minutes later the patient delivered a stillborn white male, weighing 2,069 Gm. Pituitrin was given, and the placenta was expressed intact with more than normal bleeding. Patient continued to bleed in spite of intravenous ergot and uterine massage. The cervix was examined but no lacerations were found. The uterus was immediately packed through a tubular packer. Since the patient showed signs of mild shock, 750 c.c. of glucose and saline were given, followed later by a transfusion of 500 c.c. of whole blood. She rallied rapidly and left the table in good condition; blood pressure 130/80.

At 3 A.M. the patient again went into shock. Fluids were started and another 500 c.c. of blood were given. Blood pressure 84/48, uterus was well contracted, and there was no discernible bleeding through the pack. The shock deepened and the patient did not rally. She complained only of numbness of the lower extremities. At 6 A.M. the patient was still in shock and showed signs of early pulmonary edema. About the same time slight abdominal distention was noted accompanied by lividity of the lower half of the body. Oxygen therapy was started and respiratory stimulants given. Death occurred at 10:50 A.M.

Post-mortem Examination.—(Dr. Abraham Fink, Department of Pathology, Cincinnati General Hospital.)

Anatomic Diagnosis: Rupture of the spleen with hemorrhage into the peritoneal cavity. Focal hemorrhages into the lower lobe of the right lung, mesentery, fundus of the stomach, and colon.

Gross Description: The autopsy was performed four hours post mortem. The abdominal cavity contained 600 c.c. of dark red fluid blood. The peritoneum was smooth, glistening, and pearly pink. In the upper right quadrant there was a thin fibrinous deposit on the under surface of the diaphragm and on the spleen. The organs were in their normal relationship and the large, firm uterus was intact and extended superiorly to 2 cm. below the level of the umbilicus. The heart, aorta, and lungs appeared normal except for scattered areas of hemorrhage, varying from 0.5 to 1.5 cm. in diameter in the right lower lobe of the lung. In the substance of the left diaphragm there was a circular area of hemorrhage 1 cm. in diameter.

The large, soft, opalescent red spleen weighed 625 Gm., and was covered with smooth glistening capsule. At the notch of the anterior border of the spleen there was a shallow groove extending along the diaphragmatic surface. About the midpoint of this groove there was a ragged, linear break in the capsule, measuring 1.5 cm. in length and 0.3 cm. in width. This extended for a depth of 1.2 cm. into the parenchyma of the organ. There were a few light, fibrinous strands lying on the surface of the spleen but not adherent to it, except in the region of the break. Sectioning revealed a dark, pultaceous splenic tissue.

The dark, reddish brown liver weighed 2,050 Gm. On section the tissue was brown, firm, and dripped blood. The gall bladder and pancreas were normal.

The mesentery of the small intestines contained several circular areas of hemorrhage which varied from 0.5 cm. to 1.5 cm. in diameter. Several circular areas of hemorrhage 0.5 cm. to 2.0 cm. in diameter were present in the wall of the fundus of the stomach and colon.

The kidneys, ovaries, and oviducts were apparently normal. The uterus was large, firmly contracted and measured 21 cm. by 8.3 cm. The walls were firm and pink, were intact, and measured 4 cm. in thickness. The cervical os was patulous but not lacerated. The endometrium was shaggy and dark red, and the fundus was covered by grayish stringy material.

The amorphous monster was ovular in shape, measured 5.5 by 8 inches and weighed 1¼ pounds. At the cephalic end there was a thin tuft of hair. The skin was pinkish in color but appeared thicker than normal. The consistency of the mass was that of a soft fibroid.

Pathologic Report.—(Dr. Henry Brodie, Beth Israel Hospital, New York, New York.) *Gross Examination:* The specimen which was previously fixed and partly dissected was a flat ovoid mass whose (present) dimensions were 21 by 14 by 4 cm. There were no external appendages. There was no external distinction between head, thorax, and trunk. A segment of umbilical cord 9 cm. long was attached to an umbilicated area at one edge. The entire surface of the specimen, except for a previously bisected orifice on one flat surface, was covered with skin. Brownish black hair covered less than one-third of the specimen (Fig. 1). Within the orifice were several bonelike protuberances (probably maxillae) which on incision revealed a number of nonerupted teeth. When the skin in the region of the orifice was reflected, a mandible-like bone was found, underneath which was a tonguelike structure. Behind this was a cavity covered with a smooth membrane over which hung a uvulalike structure. To either side were cartilaginous structures suggesting turbinate processes. The pharynxlike cavity seemingly ended blindly. No esophagus was recognized.



Fig. 1.—Partly dissected ovoid mass without external appendages and covered with hair at the cephalic end.

About 5 cm. below the base of the tongue a branching set of small vessels led from a second cavity surrounded posteriorly and laterally by a bony cage which was formed by an incomplete vertebral column and a number of incomplete ribs. At the inferior edge of this cavity just to the right of the midline a purplish brown structure was found 1 cm. in diameter. On section this showed the characteristic markings of suprarenal tissue. To the left of the midline was a slightly smaller similar suprarenal. Below this was a piece of enteric canal blind at both ends. At its upper end immediately adjacent to the suprarenals was a firm nodule about 6 mm. in diameter which on section suggested pancreatic tissue. The piece of enteric canal, 4.5 cm. long and 6 mm. in average diameter, had a portion of short mesentery. The only other thoracic or infrathoracic organs recognizable were three tiny yellowish gray structures, the largest of which was about 3 mm. in diameter, and all situated close to the midline.

In the umbilical cord were two blood vessels, one thick and the other thin walled. The thin-walled vessel divided after passing within the umbilicated area.

REFERENCES

- (1) *Walton, A. J.*: Brit. M. J. 22: 1496, 1928-1929. (2) *Kotschnew, M. S., and Manenkov, P. W.*: Zentralbl. f. Gynäk. 49: 3106, 1930. (3) *De Lee, J. B.*: Principles and Practices of Obstetrics, Philadelphia, W. B. Saunders Co., Chapt. 4, p. 108. (4) *Dameshek, W.*: Arch. Int. Med. 47: 968, 1931. (5) *Barcroft, T. J., and Stevens, J. G.*: J. Physiol. 66: 32, 1928. (6) *Kehrer, E.*: Zentralbl. f. Gynäk. 45: 941, 1921. (7) *Stretton, J. L.*: Brit. M. J. 1: 901, 1926. (8) *Bohler, E.*: Bull. Soc. d'Obst. et de Gynec. d'Paris 21: 141, 1932. (9) *Smith, A. H. D., Morrison, W. J., and Sladder, A. F.*: Lancet 1: 694, 1933. (10) *Burnett, E. C., and McMerrimey, W. H.*: Brit. M. J. 1: 1122, 1935. (11) *Sommer* (Berlin): Ztschr. f. Geburtsh. u. Gynäk. 116: 107, 1932. (12) *v. Hoch, R.*: Deutsche med. Wchnschr. 64: 48, 1938. (13) *Bohler, E.*: Bull. Soc. d'obst. et de gynéc. 22: 707, 1933. (14) *Serbin, W. B.*: AM. J. OBST. & GYNEC. 34: 486, 1937.

DIFFICULT LABOR DUE TO AMORPHOUS MONSTER

I. LE VINE, M.D., AND I. J. WOLF, M.D., PATERSON, N. J.

A CARDIACUS AMORPHUS is a form of essential monster born with a separate homologous twin or triplet, which is usually normal and on which it depends for its imperfect development in the uterus. Only 8 cases of amorphous monster have been reported in the American literature since 1882.¹ Most of the reports have appeared in the German literature. We have been prompted to report this case because of its rarity and the difficulty it presented in delivery.

CASE REPORT

Mrs. M. P., aged 37 years, gravida ii, had her last menstrual period on Dec. 7, 1938. Quickening was felt April 21, 1939 and her estimated confinement was Sept. 19, 1939. Her family history was negative. Four sisters and one brother were living and well. There was no history of multiple births, or the birth of monsters in her family to the best of her knowledge. Her past history was negative. Her menses began at the age of fifteen, occurring every twenty-eight days, and lasting five days with moderate flow and slight pain. She had been married four years. Her husband's health was good, and they had one child aged 2.5 years. Her previous delivery was normal and she had had no miscarriages.

The patient received routine prenatal care. Her abdomen seemed large during pregnancy but a multiple pregnancy was not diagnosed. Only one fetal heart was heard. No extra fetal mass was palpable in the abdomen. Prior to the delivery the uterus measured about six inches above the umbilicus.

The patient was admitted to the Barnert Hospital, Sept. 13, 1939, at 1:30 A.M. Her pains were irregular and by 9:00 A.M. were recurring regularly with moderate severity. At 1:20 P.M. she was delivered of a live female infant weighing 4½ pounds which presented by the breech but was delivered without difficulty. Following the birth of the baby, a mass was palpable in the abdomen, delivery of which was awaited about an hour. When this failed to occur, one ampoule of pituitrin was divided into three doses and each part was given at ten-minute intervals without effect. The patient was anesthetized and an intrauterine examination was made. A smooth rounded mass was felt which had an opening suggesting a mouth. This was grasped and delivery was attempted but was unsuccessful. Delivery was finally accomplished by making lateral incisions into the mass and placing the hooked ends of an obstetric forceps into each side. The monster was extracted in this way. A single placenta followed.

A normal amount of bleeding followed, and there were no lacerations. The mother was given sulfanilamide for a few days and recovery was uneventful. The baby was weak, nursed poorly, had facial twitching and nystagmus but left the hospital in fairly good condition on Sept. 24, 1939.

A MECHANICAL INK WRITING RECORDER SUITABLE FOR RECORDING UTERINE MOTILITY DURING PREGNANCY AND LABOR*

CON FENNING, M.D., CHICAGO, ILL.

(From the Department of Pharmacology and Physiology, University of Utah and Department of Obstetrics and Gynecology, The University of Chicago)

WHILE making capaciographic recordings of uterine activity during pregnancy and labor, it was recognized that the displacement amplitude was adequate to drive a simple mechanical lever system provided with an ink writer. No effort is made to record intrauterine tensions per se; specific efforts are made to record

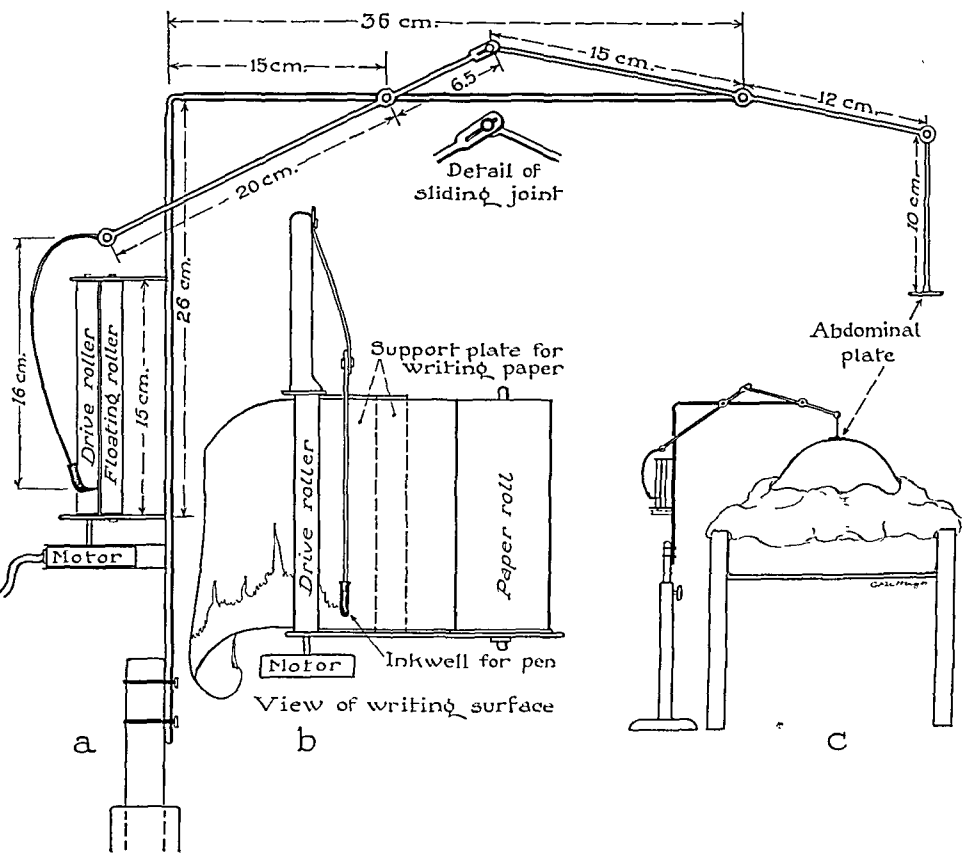


Fig. 1.

displacements, hence the use of a light lever system having an implication of four to one. Displacements associated with minor intrauterine tension changes and displacements localized in nature and not necessarily associated with intrauterine tension can be readily recorded.

The lever system is constructed of aluminum; the total weight resting upon the abdominal wall is 15 Gm. An increment of $\frac{1}{2}$ Gm. is sufficient to overcome the bearing and writing point resistance. Theoretically, with proper materials and workmanship, the total weight upon the abdomen and the force necessary to overcome

*Received for publication, April 11, 1940.

One branch, together with the thick-walled vessel, passed superiorly in the direction of the suprarenals, passing dorsal to them. The vessels then subdivided to form the many branches mentioned above. No trace of a heart was found. The second branch was almost immediately lost in a mass of fat and connective tissue in the region of the umbilicus.

The specimen had previously been incised posteriorly in the cranial region. There was revealed a shell-like skull containing a remarkably well-formed brain in which cerebral hemispheres, cerebellum, and brain stem could all be recognized. There was a tremendous dilatation of the ventricular system. A short portion of vertebral column (5 cm. long) and in its spinal canal a spinal cord, 3 cm. long, were found. A depression was found in one of the flat bones in which was some soft tissue, part of which was black and suggested retina. This last named structure lay immediately behind the external orifice. No bilaterally symmetrical structure was found. No trace of either pectoral or pelvic girdle was seen, nor any appendicular skeleton.

Microscopic Examination: Sections from the enteric canal showed tissues similar to that seen in various portions of the normal gastrointestinal tract. In one section there was an area of bronchial epithelium with underlying mucinous glands and cartilage. The tongue showed a normal histologic picture with a small island of aberrant cartilage. The pancreas was well formed with acinar duct and island tissue.

The suprarenals were well formed. One of the tiny nodules was also suprarenal tissue. The other two nodules were ovary with numerous primordial follicles. No pituitary tissue was found in numbers of sections taken from the cranial cavity. One piece proved to be ganglion tissue, presumably Gasserian ganglion.

Diagnosis: Female acardiacus amorphus with incomplete formation of the central nervous system, cranial and axial skeletons, and an incomplete enteric canal with its derivatives.

REFERENCES

- (1) *Noeggerath*: New York M. J. 35: 522, 1882 (from the description probably a fetus amorphous); *Boldt, H. J.*: Am. J. Obst. 22: 403 and 1292, 1889; *Hirst, B. C.*: Univ. M. Mag. Phil. 8: 120, 1895-1896; *Mishkin, J.*: Med. & Surg. Reporter Phil. 75: 533, 1896; *Jacobson, A. C.*: Brooklyn M. J. 11: 529, 1897; *Carey, E.*: Anat. Rec. 2: 207, 1916; *Stemons, J. M.*: Am. J. Obst. 75: 749, 1917; *Simonds, J. P., and Gowen, G. A.*: Surg. Gynec. Obst. 41: 171, 1925. (2) *Hirst, B. C., and Piersol, G. A.*: Human Monstrosities, Part 3, Philadelphia, 1892, Lea Bros., & Co., pp. 128-143. (3) *Van Tongeren, F. C.*: Zentralbl. f. Gynäk. 56: 594, 1932. (4) *Schultze, K. W.*: Monatschr. f. Geburtsh. u. Gynäk. 95: 389, 1933. (5) *Gynecology and Obstetrics*, edited by Carl H. David, Hagerstown, Md., 1934, W. F. Prior Co., Vol. 1.

Kreis, J.: *Diagnosis and Treatment of Functional Meno-metrorrhagia in Adolescence*, Gynec. et obst. 40: 48, 1939.

Kreis discusses the three types of menstrual disturbances which may arise during adolescence, namely, polymenorrhea, intercylic hemorrhage, and glandular hyperplasia. The diagnosis can only be made by curettement. The prognosis in polymenorrhea and intercylic bleeding is more favorable than it is for glandular hyperplasia. Treatment consists of the use of hemostatics, curettement, physical agents, blood transfusions and hormones, such as estrin, progesterin, insulin, gonadotropic extracts and transfusions of blood from pregnant women.

Since recurrences are frequent, especially in the cases of glandular hyperplasia, regular treatment must be instituted. The author believes that in most of these cases the etiology is more constitutional than endocrine.

The frequency of syphilis, particularly hereditary syphilis and the therapeutic success obtained with specific treatment in these cases merits attention.

Operative interference is justified only when all other forms of therapy have failed. Repeated curettements should first be done, and if these are not curative, hysterectomy is the treatment of choice. The author warns against partial, temporary, or permanent castration.

J. P. GREENHILL.

friction can be made negligible. However, an earlier model exerting 60 Gm. and having a relative high writer and bearing friction provided surprisingly good records.

A schematic view of the instrument in use is shown in Fig. 1, *c*. The assembly and measurements of the lever system are shown in *a* of Fig. 1. *b* of Fig. 1 shows the accessory equipment needed to drive the paper at a uniform rate.

Fig. 2*A* shows a typical recording obtained with the equipment. For comparison a simultaneous capnigraphic recording is also shown, Fig. 2*B*. The motility recorded is the most difficult type to record because of its low amplitude. In general, the two recordings are similar; maternal respiration, on occasion, when not masked, the maternal pulse, fetal activity, and uterine displacements are readily recognized. Minor differences, however, may be expected due to the fact that the capnigraph records the over-all abdominal displacement, whereas the mechanical approach records a point displacement.

Fig. 3 shows typical uterine displacements ordinarily recorded during early labor. Fig. 4 shows a recording in which there is rhythmic recurrence of two separate types of uterine motility in the pregnant uterus. Previous attention was called to this phenomenon.¹

SUMMARY

A simple ink writing lever system suitable for recording uterine activity during pregnancy and labor is described and actual specifications supplied. The recorder provides records which fundamentally are the equivalent of capnigraphic recordings.

REFERENCE

- (1) *Fenning, C., Davis, M. E., Adair, F. L.*: AM. J. OBST. & GYNEC. 38: 670, 1939.

A TECHNIQUE FOR THE RECTAL ADMINISTRATION OF PARALDEHYDE

PRELIMINARY REPORT

J. KOTZ, M.D., F.A.C.S., AND MORTON S. KAUFMAN, A.B., M.D.,
WASHINGTON, D. C.

PARALDEHYDE is generally conceded to be one of the safest of all the analgesic agents used in obstetrics. The analgesic and amnesic effects derived from adequate dosage are excellent. The one great disadvantage has been the difficulty of administration. Numerous methods have been devised to overcome this difficulty, but none have proved entirely satisfactory.

Paraldehyde was originally suggested in obstetrics by Davidoff and Rosenfeld,¹ who administered the drug by rectum in a small amount of olive oil. Colvin and Bartholomew² published their report shortly after and they used the same method of administration. They have since changed to the oral method.

Kane and Roth³ added benzyl alcohol, a mild anesthetic agent, to the mixture. The results were rather disappointing, at least in our hands, and benzyl alcohol is a rather toxic drug. Dr. Kane is now using a mixture of paraldehyde and port wine administered by mouth for the initial dose.

Douglas and Peyton⁴ advocated the administration of paraldehyde by mouth mixed with equal parts of aromatic elixir and chilled in cracked ice. They claimed that the action was more rapid, but admitted that vomiting frequently occurred.

DeCosta and Reese⁵ tried to overcome the nauseous taste and odor of the drug by administering it in gelatin capsules by mouth. The number and size of the capsules necessary to administer a sufficient dosage makes this method objectionable to some patients. Furthermore, when the capsules dissolved in the stomach, a burning sensation, followed by vomiting, frequently resulted.

All of the oral methods have the disadvantage of being obnoxious to smell and taste and of causing gastric irritation, which results in vomiting in a large percentage of cases.

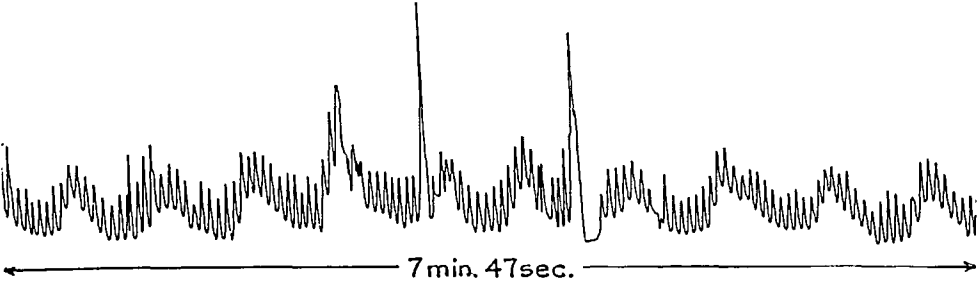


Fig. 2A.

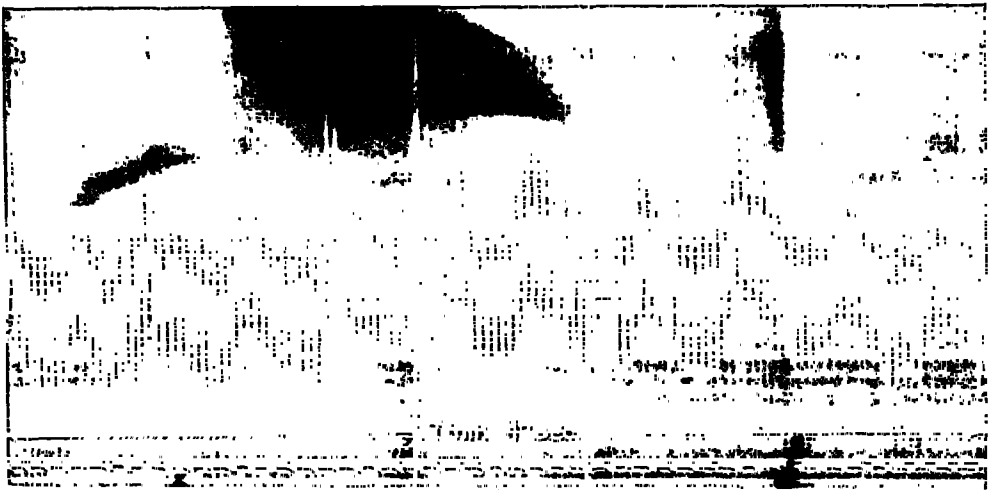


Fig. 2B.



Fig. 3.

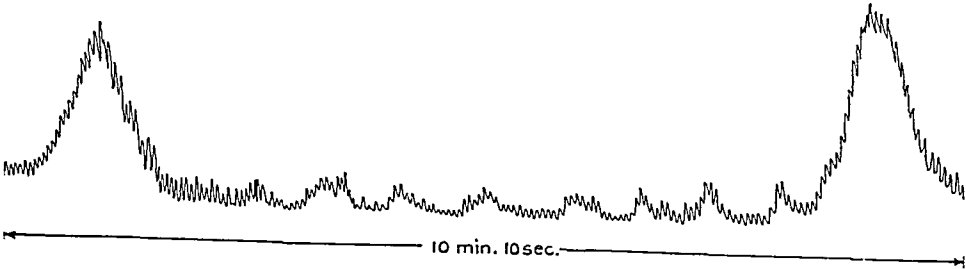


Fig. 4.

TATTOOING (PUNCTURATION) WITH MERCURY SULFIDE FOR THE TREATMENT OF INTRACTABLE PRURITUS CAUSED BY LEUCOPLAKIA-KRAUROSIS VULVAE

ROBERT TURELL, M.D., NEW YORK, N. Y.

(From the Gynecological Service of The Mount Sinai Hospital)

TATTOOING with mercury sulfide has been successfully employed for the treatment of pruritus ani,^{1, 2} and for pruritus perinei caused by an extension of the perianal itching.³ Because of the similarity in the histologic appearance of pruritus vulvae and pruritus ani,⁴ it was decided to investigate the value of this procedure in the treatment of the former condition.

This report concerns the successful employment of tattooing with mercury sulfide for the treatment of intractable pruritus caused by leucoplakia-kraurosis, which had not been controlled previously by partial vulvectomy and four additional surgical procedures.

CASE REPORT

L. S., a 32-year-old white woman, gravida and para iii, was admitted to the hospital Jan. 15, 1936, because of intense pruritus vulvae and ani. The menstrual periods were regular and normal. She had been seen in the Out-Patient Department Jan. 6, 1934, because of constipation, pain on defecation, and pruritus ani. At that time rectal examination revealed tenderness on digital exploration as well as perianal and perineal fissures. Late in 1935 there was observed an atrophic vaginitis with maceration of the labia, which had failed to respond to conservative treatment. Physical examination on this admission was normal except for atrophy with fissuring and maceration of the tissues involving the clitoris, the upper margin of the urethra, the labia minora, the fourchette, and the perineum. In view of the fact that the intense pruritus was not relieved by estrogenic therapy and hygienic measures, a partial vulvectomy was performed without removing the perineal skin. Histologic examination of the excised tissue showed hyperkeratosis, chronic inflammation, and disappearance of elastic fibers. This histologic appearance was regarded as compatible with the diagnosis of leucoplakia and kraurosis.

The patient was readmitted to the hospital May 15, 1936, because of pruritus ani and perinei of increasing severity. On examination there was no change in the pathologic process of the perineum; there was no evidence of recurrence at the site of vulvectomy. The perineal skin and subcutaneous tissue were removed three days later. The histologic examination of the excised tissue showed leucoplakia and chronic inflammation.

Mild pruritus in the perineal and perianal region continued. In February, 1937, there was observed a recurrence of the original pathologic process in the perineum, accompanied by a fissure extending to the anal orifice. Five weeks later, the patient was readmitted to hospital where the lesion in the perineum was removed. Examination of the excised tissue revealed histologic changes consistent with the diagnosis of leucoplakia and chronic inflammation.

The patient remained well for about two months, and was again admitted to hospital Jan. 26, 1938, because of pruritus and a burning sensation more intense on the left side of the introitus. Examination revealed a thickened and a yellowish white area with deep fissures in the perineum, and atrophy along the left side of the introitus, extending to the anal region. The vagina admitted two fingers, was soft, and resilient. At this time the involved tissues of the left side of the introitus and of the perineum were removed. The histologic examination of the excised tissue showed leucoplakia and kraurosis.

The patient remained well until June, 1938 (a period of four months), when she experienced a recurrence of the itching and burning in the introitus, the intensity of which was increased during the menses. Examination showed a normal uterus and

All of the rectal methods of administration have the disadvantage of causing a severe burning, and frequently an uncontrollable desire to expel the medication.

In order to overcome this effect, we have devised a method of administration which we feel is distinctly superior to any yet advocated. Our routine is as follows:

1. Soda bicarbonate enemas until returns are clear.
2. Morphine sulfate gr. $\frac{1}{6}$ (hypodermic) and 5 c.c. of 1:1000 solution of nupercaine instilled into the rectum with an ordinary bulb syringe.
3. Nupercaine ointment smeared around the anus.
4. Ten to fifteen minutes later, paraldehyde drachms vi-viii, preceded and followed by drachm 1 of mineral oil or olive oil.
5. Paraldehyde, drachms iii-iv whenever the patient begins to arouse with her pains.

COMMENT

Nupercaine (Alpha-Butyl-Oxycinchonic acid diethyl-ethylene-diamide hydrochloride) is a relatively nontoxic, rapid acting, topical anesthetic which produces an intense and prolonged local anesthesia. It does not irritate the rectal mucosa, or cause any impulse to defecate. It is much less toxic than cocaine, and much less expensive than some of the equally effective drugs such as butyn or metycaine. By administering it ten to fifteen minutes before the paraldehyde, we give it ample time to completely anesthetize the mucosa of the lower rectum. By anointing the anus with nupercaine ointment, we avoid the burning caused by the drops of paraldehyde remaining in the tube as it is withdrawn.

The administration of morphine ten to fifteen minutes before the paraldehyde, allows time for absorption of the drug. Morphine lessens peristalsis and relaxes the smooth muscle of the gut, thus inhibiting defecation. At the same time, the burning sensation is lessened by the analgesic effect of the morphine.

The chance for error is much lessened by this method, because each ingredient is administered separately, and may be checked immediately before its introduction.

RESULTS

This method has been used in 30 cases. In 21 cases, the results were excellent, none of these patients complaining of either burning or the desire to defecate. All of the remaining 9 patients had an impulse to expel the drug, and 4 of these had a burning sensation. One of these, a primipara with the head low, 5 cm. dilated, and having rather severe pains every three minutes, expelled the initial dose.

The duration of the unpleasant symptoms was much less than is usually seen with similar doses of paraldehyde by rectum, nor were the symptoms nearly so severe.

The best results were obtained in patients in early labor, where the need for immediate analgesia is not urgent, and the pains are not expulsive in character. In the latter part of the first stage, or in the second stage, better results are obtained by giving the dose of paraldehyde while the patient is under light ethylene anesthesia. The ethylene is continued for ten to fifteen minutes after the administration to allow the paraldehyde to become partially absorbed.

SUMMARY

We present here a new technique for the rectal administration of paraldehyde. The method is safe, inexpensive, and effective in relieving the burning sensation, and the desire to expel the medication, which usually accompanies the rectal administration of the drug.

The technique has been used in 30 cases, with excellent results in 21, nine desired to expel the medication, and 4 had some burning. One patient expelled her initial dose.

REFERENCES

- (1) *Rosenfeld, H. H., and Davidoff, R. A.*: New England J. Med. 207: 366, 1932.
- (2) *Colvin, E. D., and Bartholomew, R. A.*: AM. J. OBST. & GYNEC. 35: 589, 1938.
- (3) *Kane, H., and Roth, G. B.*: Anesth. and Analg. 16: 121, 1937. (4) *Douglas, L. H., Peyton, F. W., and Siau, J. R. S.*: AM. J. OBST. & GYNEC. 35: 636, 1938. (5) *DeCosta, E. J., and Reis, R. A.*: AM. J. OBST. & GYNEC. 34: 448, 1937.

REFERENCES

- (1) *Hollander, E.*: Arch. Dermat. & Syph. 38: 337, 1938. (2) *Turell, R., Buda, A. M., and Marino, A. W. M.*: Ibid. 41: 521, 1940. (3) *Turell, R.*: To be published. (4) *Montgomery, H.*: Personal communication to the author. (5) *Myers, H. Russell, and Turell, Robert*: Unpublished data.

876 PARK AVENUE

A NEW SCISSORS FOR INCISING THE UTERUS IN CESAREAN SECTION*

BERNARD L. CINBERG, M.D., NEW YORK, N.Y.

IN performing cesarean section, most operators open the uterus by making a small incision with a scalpel and completing it with a bandage scissors. This type of scissors is used to protect the fetus from injury by the edge of a scalpel or by the points of an ordinary scissors.

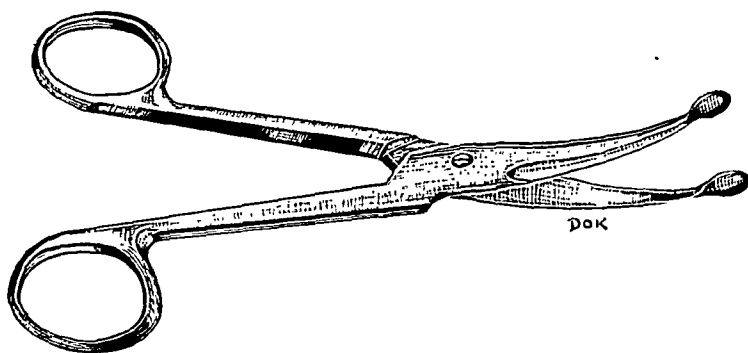


Fig. 1.

The past two years have seen a rapid rise in popularity of the transverse uterine incision. Here, it is important to curve the ends of the incision upward, to avoid the uterine arteries. To make this "U" incision more easily, some surgeons employ a "curved on the flat" Mayo scissors.

We have devised a scissors which utilizes the important features of both these instruments. Its blunt points and "side-ways" curve, make it the ideal instrument for transverse uterine incisions.

50 EAST 78TH STREET

*This instrument is manufactured by N. S. Low & Co., Inc., New York City.

adnexa. There was atrophy of the skin adjacent to the clitoris and recurrence of the kraurotic-like process at the vaginoperineal junction. As a result of the previous operative procedures the posterior vaginal mucosa had extended over the upper one-third of the perineum. At its distal portion, it was partially epithelialized and atrophic. In the intergluteal region there was a bilateral, symmetrical area of parchment-like atrophic skin which extended to and encircled the anus. On October 19, 1938, the atrophic skin of the subclitoric region, and the kraurotic-like process at the vaginoperineal junction were excised. Fragments of the excised skin showed areas of chronic nonspecific inflammation without evidence of kraurosis. November 10, several Thiersch grafts were implanted upon the granulating perineal area.

There was continuous itching and soreness in the region about the left side of the introitus and over the entire perianal area. Re-examination June 5, 1939, showed a narrowing of the introitus and a whitish plaque about the anterior commissure. The skin of the posterior commissure, the terminal inch of the mucosa of the vagina, and the skin of the perineum extending to and surrounding the anal orifice had changed to a white, thick, cornified plaque. The perianal skin was tense, shiny white in appearance, and parchment-like in consistency. The crural folds presented the same appearance and were also fissured.

Physical examination was otherwise normal; there was no evidence of disease of the nervous system to account for the local manifestations. The essential laboratory tests were negative. The dermatologist (Dr. L. Chargin) agreed that tattooing with mercury sulfide should be given a trial.

On June 7, 1939, the perianal and the perineal regions were tattooed with mercury sulfide under infiltration anesthesia, using 1 per cent solution of procaine hydrochloride, according to the technique described in another communication.² Seven days later, the vulva was similarly tattooed with mercury sulfide under avertin supplemented by infiltration anesthesia. One month later, the skin about the introitus and in the perianal region, with the exception of the perineal area, was normal in appearance. At the time of writing (a period of over nine months), the patient has remained free of pruritus in spite of the presence of moderate excoriation of the perineum. The latter is believed to be caused by a continuous escape of vaginal discharge which has not been treated because the patient prefers to leave "things well enough alone."

DISCUSSION

The results obtained in this patient seem to indicate that tattooing with mercury sulfide is advisable for the treatment of this type of lesion in selected cases. It is still unexplained how mercury sulfide deposited in the corium by tattoo acts in relieving localized pruritus.³ Control studies have shown that mechanical trauma alone as produced by the tattooing machine without the use of mercury sulfide is ineffectual in controlling pruritus and permanently.² It is likely that the intracutaneous deposit of mercury sulfide produces a degenerative effect on the cutaneous terminal nerve endings and twigs, altering their capacity to respond to normal stimuli. Study of the changes in the cutaneous sensory modalities thus produced is in progress.⁵

It is believed that the alteration in the cutaneous modalities is proportional, within limits, to the amount of the intracutaneous deposit of mercury sulfide. This belief is rendered more likely by the following observation: In an instance of pruritus and,³ unilateral recurrence of pruritus was noted in the particular area where a smaller intracutaneous deposit of mercury sulfide was made as indicated by a lighter red color on that side. A study of the status of the cutaneous sensory modalities disclosed that the opposite perianal area which was adequately tattooed and free from pruritus had fewer nerve endings capable of responding to tactile and painful sensations.

SUMMARY

A patient with intractable pruritus caused by leucoplakia-kraurosis was successfully treated with the intracutaneous deposit of mercury sulfide by tattoo, after a partial vulvectomy and four subsequent surgical procedures for the removal of involved or recurrent areas of skin had failed to control the distressing pruritus.

the fimbriated end of the right tube was a cyst of Morgagni. The ovarian tumor was removed, as well as the cyst of Morgagni. The abdomen was closed in the usual manner, and the mother left the operating room in good condition.

Puerperium was essentially normal, except for a postoperative rise of temperature on the first and second days to 102°F., and the pulse was 120, which returned to normal on the third day and remained so throughout her stay in the hospital. Abdominal wound healed by primary intention, and mother was discharged on February 7, fifteen days postoperatively, in good condition. Her blood pressure had returned to normal and at the time of discharge was 130/80. Urinalysis at discharge was negative.

2309 EUTAW PLACE

THE PREVENTION OF POSTOPERATIVE TRAUMATIC AND CATHETER CYSTITIS

JAMES R. GOODALL, M.D., AND LOUIS J. QUINN, M.D., MONTREAL, QUE.

(From St. Mary's Hospital)

THIS problem has occupied our attention for many years, and after trial of numerous methods with varied success, we have finally come to the conclusion that the one herein described has given us almost uniformly good results with a minimum of discomfort to the patient, and with the least number of unpleasant sequelae.

We have felt all along that we confer a doubtful benefit if, in curing a patient's pelvic pathology or repairing her hernia of pelvic organs, we leave her with a residual cystitis, or, worse still, with a uni- or bilateral pyelitis.

These are the common complications of extensive repair operations and, in spite of all our previous study in this important matter, these sequelae were all too common. The great majority of repair cases come to operation in the later years of their life. Their pelvic tissues are postmenopausal in their atrophy and lowered in their healing power. Consequently, any postoperative inflammation in the nature of cystitis is often hard, sometimes impossible, to cure.

Pyelitis following repair operations upon the anterior vaginal wall is also an all-too-common postoperative complication. The cause of this is not hard to find. If one examines the interior of the bladder after an extensive radical cure of cystocele, the bladder mucosa is thrown into folds due to the plication of the redundant mucosal lining of the bladder, which has stretched to keep pace with the progressive descent. As a consequence the circulation of the bladder is interfered with, and local edema often occurs. Catheterization, therefore, even when carried out with meticulous aseptic care, may result in implanting an infection upon these adult, atrophic, strangulated tissues. Moreover, postoperative catheterization of the ureters in extensive repair cases frequently demonstrates a kinking of the vesical ends of the ureters, owing to suturing the cardinal ligaments in front of the cervix, and a consequent great or small amount of ureteral urinary retention, with consequent frequency of pyelitis. Our study shows that in the vast majority of cases of postoperative urinary retention there is a nervous or traumatic inhibition of bladder function and, frequently, a degree of obstructive ureteral flow. To overcome this in great part, if not wholly, it is advised to keep the patient in bed during the period of preoperative care and study of the case, when the blood, blood sugar, and other tests are being carried out. Do not allow her bathroom privileges, so that she becomes inured to the use of the bedpan for evacuations before the added inhibition of the operation. We have found that the number of cases of urinary retention is inversely as the length of time that the patient is thus educated. At the time of operation, when any extensive operation is performed upon the anterior vaginal wall, and thereby the foundations of the bladder are disturbed, a slashed Malecot

BRENNER TUMOR OF THE OVARY COMPLICATING LABOR

ISADORE A. SIEGEL, A.B., M.D., BALTIMORE, Md.

(*From Department of Obstetrics, Franklin Square Hospital*)

THIS case of Brenner tumor of the ovary blocking the pelvis and preventing normal delivery is reported because it is a rare tumor, complicating pregnancy and producing dystocia. Novak and Jones report three cases of Brenner tumors complicating pregnancy in which one patient was operated upon when she was four months pregnant; another in which the diagnosis of pregnancy was made only by the finding of decidual tissue after curettage; and a third case in which the patient had six previous pregnancies, five terminating in abortions, and one in a premature stillbirth at the seventh month. It is interesting, therefore, to record this case as complicating a full-term pregnancy.

The patient, a 27-year-old primigravida, was admitted to the Franklin Square Hospital on Jan. 17, 1940. External pelvic measurements were all normal. Last menstrual period occurred on April 13, 1939 and the expected date of confinement was Jan. 20, 1940. Prenatal course was essentially normal until one week prior to hospitalization, when the patient developed an elevation of blood pressure for which she was treated at home by diet, rest, and catharsis. On the day of admission to the hospital the patient's blood pressure at home was said to be 190/110 and she complained of headaches and vomiting.

On admission her blood pressure was 150/100; urine showed a trace of albumin; duration of pregnancy was at term. Fetal heart was heard in the lower left quadrant, presenting part was at the superior strait. There was no edema of the face nor of the lower extremities, and rectal examination showed the cervix to be completely effaced, and canal closed; head not engaged. Blood chemistry: nonprotein nitrogen, 30.6 mg.; uric acid, 2.8 mg.; creatinine, 1.5 mg.; sugar, 102 mg.; Wassermann, negative; Hg, 85 per cent.

The patient was treated conservatively. She was put on a low protein, salt poor diet, and fluids forced to 3000 c.c., including carbohydrate drinks. She was given $\frac{1}{4}$ gr. of morphine at once and 1 gr. of luminal four times daily. One ounce of magnesium sulfate every morning. The blood pressure readings were taken every three hours. Under this treatment her systolic blood pressure had a tendency to fall, but the diastolic remained rather stationary, around 100. Blood pressure was stabilized at 140/100. Urine subsequently showed no albumin, headaches disappeared, and the patient appeared comfortable. After three days of conservative treatment, since the patient was at term and her blood pressure was remaining stationary, medical induction of labor was instituted by the use of castor oil, quinine, and hot enema, but was ineffectual. On the following day medical induction was continued by the use of pitocin, 2 min. every half hour for three doses. This, likewise, was unsuccessful. On January 23, induction of labor by rupturing the membranes was considered. At this time it was found that there was a mass lying in the pelvis below the promontory of the sacrum about 5 by 4 inches, which felt rather doughy and could not be pushed out of the pelvis. The cervix was above this mass, the canal was completely effaced, and the os about 2 to 3 cm. dilated. The head was not engaged. On rectal examination this mass was found to lie outside the rectum. A diagnosis of ovarian tumor or fibroid, blocking the pelvis, was made.

The following day a low cervical cesarean section was performed, and the patient delivered a living female child, weighing 7 pounds 4 ounces. The baby was found lying in left sacroanterior position and slightly transverse. Following the completion of the closure of the low uterine segment, the left ovary was examined and found to be normal. The tumor lying in the pelvis was easily removed and found to be a solid tumor of the right ovary rather larger than was estimated at the time of pelvic examination, and had a long pedicle; in addition to this, on

Special Article

"ANESTHÉSIE À LA REINE"

A CHAPTER IN THE HISTORY OF ANESTHESIA

HERBERT THOMS, M.D., NEW HAVEN, CONN.

QUEEN VICTORIA was delivered of Prince Leopold, her eighth child, on April 7, 1853. She was attended in confinement by Sir James Clark, Bart. M.D., and John Snow, M.D. The latter was present in the capacity of anesthetist, and the event is historical in the annals of obstetrics because Her Majesty was the first crowned head to receive the benefits of anesthesia in childbirth. Chloroform was administered on a handkerchief in 15 minim doses, the inhalation lasting fifty-three minutes. The drug was administered intermittently and induced what we think of as "inhalation analgesia," for the patient was not unconscious at any time. The Queen expressed herself pleased with the effect. Her attendant, Sir James Clark, well appreciated the importance of the event and the effect that it would have in influencing the establishment of anesthesia in obstetrics, for shortly afterward he wrote to James Y. Simpson, "I know this information will please you, and I have little doubt it will lead to a more general use of chloroform in midwifery practice in this quarter than has hitherto prevailed." Today the event is memorialized in obstetric parlance by the phrase "*anesthésie à la reine*," which signifies the peculiar type of intermittent inhalation anesthesia which has become so useful in obstetric practice.

Other than the facts stated above not much was recorded of the details of the birth. We do know that Dr. Snow had previously been consulted on the occasion of the birth of Prince Arthur in 1850 but had not been called in to render service. We also know that previous to the birth of Prince Leopold he had had an interview with the consort, Prince Albert, and was much impressed with the kindness and intelligence which that gentleman showed concerning the scientific points which formed the subject of their conversation. Later, in 1857, the Queen was again to receive the ministrations of Dr. John Snow at the birth of Princess Beatrice.

Both James Clark and John Snow had interesting and notable careers, the latter being an important figure in the annals of anesthesia and epidemiology, and the former the most important physician in court circles in his day. When James Clark, in 1834, was appointed to the post of physician to the Duchess of Kent, the Queen's mother, something of a sensation was created for a biographer states that the Fellows of the exclusive College of Physicians, "looked on the appointment of a northern graduate much as the bench of bishops might resent the intrusion of a Dissenter." Clark was without question "northern" for he had been born in Banffshire, Scotland, and had been educated at Aberdeen and Edinburgh. From the latter institution he had been granted the M.D. degree in 1817. Two years later he went to Italy and settled in Rome. It is gratifying to learn that

catheter dipped in liquid paraffin is inserted into the bladder and the outer end of the catheter is clamped with an artery forceps (Fig. 1) or screw clamp, and the latter is pinned to the abdominal binder so as to allow considerable slack in the catheter. In this manner, the patient can move about in bed without discomfort. The forceps is released every three hours and the urine drawn off. This alternate emptying and filling of the bladder allows the intravesical portion of the catheter to move, and prevents the constant impinging of this portion upon a fixed spot of the trigone, as happens when continuous drainage over the side of the bed is employed. Continuous drainage is used only in cases where damage to the *continuity* of the vesical mucosa is known or suspected. Moreover, by this method, the alternate emptying and filling of the bladder helps to overcome any muscular paresis which may have resulted from nerve trauma. The patient is then given 4 tablets of 5 gr. each

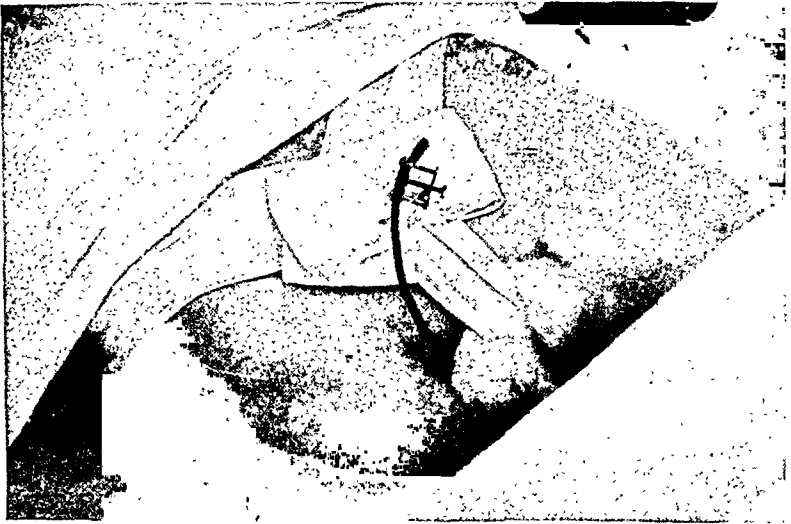


Fig. 1.—Catheter and screw clamp in situ. Fixation to binder by means of safety pin.

of neoprontosil daily. Some patients cannot swallow these. Then they may chew them, which colors the mouth and lips a bright red. In cases of emesis or intolerance of the drug, owing to gastric upset, the aseptic solution of neoprontosil may be used intramuscularly in doses of 10 c.c. twice daily. The urine soon takes on a distinct orange color, and we have noted uniform freedom from purulent infection. The catheter is left in situ from three to five days. Twenty-four hours before removing it, the patient is given 3 doses of thiamin chloride, each of 1,660 international units, subcutaneously or intramuscularly, to stimulate involuntary muscle activity. The action of vitamin B₁ upon an involuntary muscle of the various viscera is well known.

It is rare that retention follows this procedure and the results of this treatment, as regards both the incidence of postoperative cystitis and pyelitis even in the oldest of patients, have been uniformly gratifying, and recoveries have been consequently much smoother and free from the immediate discomforts of frequency and pain, and equally, from the remote consequences of pyelitis and cystitis.

1472 SHERBROOKE STREET

UNIVERSITY OF WASHINGTON
SCHOOL OF NURSING
REVIEW DIVISION

ing surgeon in London, Liston, recognized his ability and as a result he became the leading anesthetist in that city. When chloroform was discovered he made extensive animal experiments with the new drug and gave up his predilection for ether. For ten years preceding his death he is said to have averaged 450 administrations yearly.

Snow's chief work on anesthesia was published shortly after his death in 1858. This work, *Chloroform and Other Anaesthetics*, shows his fine scientific mind and his wide experience in the subject. The chapters dealing with parturition are of definite interest to us for they show how well he understood this field. He writes, "The most usual time when the accoucheur and I have determined that the inhalation should be commenced, has been when the os uteri was nearly dilated to its full extent, and the pains were taking on an expulsive character. . . . In such cases when it has been determined to resort to inhalation the moment to begin is at the commencement of a pain; and the chloroform should be intermitted when the uterine contraction subsides, or sooner if the patient is relieved of her suffering." We find here also this fine description of the procedure which is the title of this paper. He writes:

"The effects of chloroform on the brain should not be carried during labour beyond what I denominate the second degree of narcotism, or that condition in which the mental functions are diminished, but not altogether suspended, except when the effect of the vapour is associated with natural sleep. The patient under the influence of chloroform to this extent, has no longer a correct consciousness of where she is, and what is occurring around her, but is capable of being aroused to give incoherent answers, if injudiciously questioned. In this state, the patient will sometimes assist the labour by bearing down voluntarily, if requested to do so, and be otherwise obedient to what is said; and by withholding the chloroform for a few minutes, she at any time becomes quite conscious. As a general rule, it is desirable not to hold any conversation whilst the patient is taking chloroform, in order that her mind may not be excited. The plan mentioned above, of giving the chloroform very gently at first, also has a tendency to prevent its causing mental excitement, the patient coming gradually under its effects. In surgical operations, excitement of the mind can nearly always be avoided by carrying the patient pretty rapidly into a state of insensibility, in which the mental functions are necessarily suspended. But in the practice of midwifery, it is not allowable to cause a state of coma or insensibility, except in certain cases of operative delivery, hereafter to be mentioned."

This author's scientific approach to the problems of anesthesia is evidenced by his many experiments with other gases. His attention was also drawn to local anesthesia and he performed experiments with freezing mixtures, including the use of solid carbonic acid as applied to the skin. His biographer Richardson describes him as, "of middle height, of somewhat slender build, and of sedate expression. His long life in comparative student loneliness had made him reserved in his manner to strangers. . . . He kept a record of all his experiments and short notes of observations made by his friends."

It may be interesting for us to consider some of the historical facts concerning anesthesia in obstetrics and in particular of intermittent anesthesia as applied to normal labor. The first application of inhalation anesthesia was that made by James Y. Simpson on Jan. 19, 1847, the details of which were published in *The Edinburgh Monthly Journal of Medical Science* in February of that year. The case was that of a lame woman, a gravida ii, who presented a badly distorted pelvis and whose first pregnancy had been ended by craniotomy after a four-

while practicing here he devotedly attended John Keats during the poet's last illness. In 1826 Clark decided to remove to London and while on his way thence, at Carlsbad he had the fortune to meet Prince Leopold of Belgium. Here the Prince found the young physician much interested in the therapeutic uses of the waters, and on his return to London appointed him his physician. Later at his recommendation Clark was appointed the physician to his sister, the Duchess of Kent.

When the young Queen ascended the throne, the story is told that the Premier presented Her Majesty with a list of physicians, at the very bottom of which was James Clark. She is reported to have taken a pen and crossed out the name, rewriting it at the top of the list.

As physician to the Queen, James Clark had a notable and influential career, and it was said that, with Sir Benjamin Brodie, he was one of two men through whom the influence of the medical profession was chiefly exerted on the state. At one time, however, he became intensely unpopular, owing to his supposed conduct in the case of Lady Flora Hastings. The growth of a fatal abdominal tumor had led to the unjust suspicion that this unmarried court lady was pregnant. In reviewing the facts of the case it seems clear that if the advice and counsel of Sir James had been followed from the start a very troublesome episode might have been avoided. The fact that the lady would not allow an abdominal examination until some weeks had passed gave the scandal mongers time for their ghastly work, and both the doctor and the court were subjected to a degree of scurrility which may be somewhat judged by the amount of literature on the subject which was produced. It is gratifying to note that "long before his death almost everybody knew, more or less distinctly, that he had been wrongly blamed." In addition to the important influence which James Clark had on the affairs of state, he was recognized as an authority on climate in its relation to disease and published two works on the subject. In 1870, at the age of 81, Sir James Clark died.

The career of John Snow was singularly different from that of Clark. Born in York in 1813, his relatively short life of 45 years was filled with scientific achievement. His biography by Sir Benjamin Ward Richardson is entitled, "John Snow, M.D. A Representative of Medical Science and Art of the Victorian Era." His signal contributions to epidemiology can merely be mentioned here, but it is significant that in 1936 a reprint of two of his papers on cholera was published in book form by The Commonwealth Fund. In the introduction by Wade Hampton Frost, we find these words, "Some part of Snow's conception that cholera was due to a specific micro-organism, an obligate parasite, propagating only in the human intestinal tract and disseminated by the ingestion of excreta, was expressed by a number of contemporary writers; but seldom if ever was the whole idea expressed, and no one else followed it through to such full development."

Snow's interest in anesthesia had been somewhat prepared before its announcement in 1846. For some time he had been engaged in experiments on respiration and asphyxia, and five years before that event he had published a paper entitled "Asphyxia and on the Resuscitation of Newborn Children." The first ether anesthetics in England were not too successful but Snow brought the administration to perfection by the invention of an inhaler. In a short time the lead-

"To the Editor of the Boston Medical and Surgical Journal.

"Dear Sir:

"On the seventh instant, I administered the vapor of ether in a case of natural labor. The patient was in good health, and in labor of her third child. Five and a half hours having elapsed from the commencement of labor, her pains, which had been light, but regular, becoming severe, the vapor of ether was inhaled by the nose, and exhaled by the mouth. The patient had no difficulty in taking the vapor in this manner from the reservoir, without any valvular apparatus.



N. C. Keep

Fig. 1.—N. C. Keep. (Printed, by permission, from Hapgood: *History of the Harvard Dental School.*)

"In the course of twenty minutes, four pains had occurred without suffering; the vapor of ether being administered between each pain. Consciousness was unimpaired, and labor not retarded. Inhalation was then suspended, that a comparison might be made between the effective force of the throes with and without the vapor of ether. No material difference could be detected; but the distress of the patient was great. Inhalation was resumed; but the progress of the labor was so rapid, that

day labor. Under total anesthesia the second labor was completed by Simpson by a difficult version and extraction. The inhalation lasted twenty minutes.

In March of the same year Simpson published a paper, "On the Inhalation of Sulphuric Ether in the Practice of Midwifery." In a footnote he wrote, "I have during labor, kept patients under its influence for upwards of half an hour. In exhibiting it, the first or exhilarating stage of its effects should be passed through as rapidly as possible." Later in this year on the first of December Simpson read a paper at the Medico Chirurgical Society of Edinburgh on, "Superinduction of Anaesthesia in Natural and Morbid Parturition; with cases illustrative of the use and effects of Chloroform in Obstetric Practice." At that time he stated that since the latter part of January he had employed anesthesia with few exceptions in every case of labor which had been under his care and had kept up the anesthetic state from a few minutes to a number of hours. Under Case VI of this series we find a statement which seems illustrative of the procedure which he had adopted for normal labor. He writes, "She lay as usual like a person soundly asleep under it, and I was now able without any suffering on her part, to increase the intensity and force of each recurring pain, by exciting the uterus and abdominal muscles through pressure in the down part of the vagina and perineum." It seems quite evident in this case that voluntary efforts on the part of the patient were in abeyance and that unconsciousness was complete. That this method of procedure was Simpson's usual practice seems further borne out by his summary of cases in which he expresses himself, "the preceding instances, afford perhaps, a sufficient number of examples of the use of chloroform in natural labor. . . . The mothers instead of crying and suffering under the strong agonies and throes of labor have lain in a state of quiet placid slumber, made more or less deep at the will of the medical attendant, and, if disturbed at all, disturbed only unconsciously from time to time by the recurring uterine contractions producing some reflex or automatic movements on the part of the patient—like those of a person moving under any irritation of the surface, or from the touch of another, though still in the state of sleep."

Here again the inference is plain that consciousness was abolished by the anesthetic and that voluntary efforts on the patient's part were not used. This same concept is again seen in his paper of December, 1847, on the "Anaesthetic and Other Therapeutic Properties of Chloroform." He writes, "A few inhalations given then, and repeated with each recurring uterine contraction, keeps the patient in a state of unconsciousness; and this condition may be easily maintained for hours by administering in this way the chloroform vapor with each pain, and withdrawing it entirely during each interval." It is apparent that this method of anesthesia is essentially different from that described above by Snow and from that administered by him to the Queen, who "was not unconscious at any time."

From the evidence at the disposal of the author of this paper it seems quite clear that the first description of "anesthésie à la reine" is to be found in the account of the first case of anesthesia in labor which occurred in the United States. In the *Boston Medical and Surgical Journal* for April 14, 1847, the following letter from Dr. N. C. Keep is an important record.

practiced dentistry in Boston, devoting himself particularly to mechanical dentistry, the forerunner of prosthesis. When the first faculty of the Harvard Dental School was appointed on Nov. 30, 1867, Nathan Cooley Keep, M.D., was elected Professor of Mechanical Dentistry, and on March 19, 1868, he was elected the first Dean of the Dental School Faculty. His career as a leader in the development of his profession is well known and does not need further elaboration here, but his part as a witness in one of the great murder trials of his day is of interest. It was upon his testimony that Professor Webster was convicted of the murder of his colleague, Professor Parkman. Soon after the murder, a set of false teeth was found supposed to have belonged to Parkman. Some years before Keep had made a set for Parkman and when the molds for this set were produced in the courtroom it proved the ultimate dramatic note in the trial which convicted Webster. After the murderer had killed his victim he burned the body in the furnace and the only remaining evidence which withstood the flames was the set of porcelain teeth.

As a recognition of his services to dentistry, Dr. Keep was awarded the honorary degree of D.M.D. by Harvard in 1870, and previously he had been honored by the honorary degree of D.D.S. by the Baltimore College of Dental Surgery in 1843. On March 11, 1875, seven years after the establishment of the Harvard Dental School, its founder and first Dean, Nathan Cooley Keep died.

Such in brief is the story of an obstetric expression, "anesthésie à la reine," a phrase which is found chiefly in textbooks and whose meaning is much better defined by the term *obstetric inhalation analgesia*. That the latter procedure is a definitely obstetric technique there is but little question, and when we consider its evolution it seems obvious that it should be a natural development in the application of anesthesia to obstetrics. That it was an early development was undoubtedly due to its use as a technique in dentistry by a man who was both a physician and a dentist and whose scientific mind led him to apply it at the first opportunity in an untried field. In the history of anesthesia, as applied to obstetrics, Nathan Cooley Keep was a real pioneer.

REFERENCES

- Channing, W.: A Treatise of Etherization in Childbirth, Boston, 1848. Duns, J.: Sir James Y. Simpson, Bart., Edinburgh, 1873. Gordon, H. L.: Sir James Young Simpson, N. Y., 1897. Hapgood, R. L.: History of the Harvard Dental School, Boston, 1930. Keep, N. C.: Boston M. & S. J. 36: 199, 1847. *Idem*: *Ibid.* 36: 226, 1847. Munk, Wm.: The Roll of the Royal College of Physicians of London, 1878. Simpson, E. B.: Sir James Y. Simpson, Edinburgh, n. d. Simpson, J. Y.: Account of a New Anaesthetic Agent, etc., Edinburgh, 1847. *Idem*: Superinduction of Anaesthesia in Natural and Morbid Parturition, Boston, 1848. Snow, J.: Asphyxia and the Resuscitation of Stillborn Children, Lond. Med. Gazette, 1841; 29, 222. *Idem*: Lancet 1: 177, 1848. *Idem*: London M. J. 1: 50, 1849. *Idem*: On Chloroform and Other Anaesthetics, London, 1858. Snow on Cholera (The Commonwealth Fund), New York, 1936.

time could not be found for sufficient inhalation to bring the system perfectly under its influence: still the sufferings of the last moments were greatly mitigated. From the commencement of the inhalation to the close of the labor, thirty minutes. Number of inhalations, five. No unpleasant symptoms occurred and the result was highly satisfactory.

Yours &c

N. C. Keep"

"Boston, April 10, 1847.

This case which occurred less than three months after Simpson's first administration is clearly that in which inhalation analgesia was used. Walter Channing, America's champion of anesthesia in childbirth, sensed the importance of the observation and commented upon it as follows, "It is the first case in which sulphuric ether was exhibited by inhalation in labor in this country. Besides its historical interest, it has in itself much which is practically useful. Thus, ether was inhaled 'between each pain.' Consciousness was unimpaired, and labor not retarded."

The administration of ether as an anesthetic was not a novel experience for Dr. Keep, for he had for some time been using ether in the practice of dentistry, in which he was then engaged. In a previous communication he had written concerning its administration, "In the last 200 cases (nearly all intelligent persons, capable of accurate observation) I have not known one who was not conscious of existence, of time, and of the operation that was being performed, but though the intellect was nearly or quite undisturbed, the sensibility to pain has been uniformly greatly diminished, and generally entirely lost. . . . I have extracted teeth for persons of all ages, from 6 to 60. . . . I have destroyed the entire nerve of the tooth for a number of persons while under the influence of the vapor. . . . I entertain the opinion that the inhalation of the vapor of ether, when administered in a proper manner, by a person understanding it, and capable of regulating its quantity and power, as every person using it should be able to do, is safe, and will greatly mitigate, and in most cases take away all pain in dental and surgical operations." It is clear from this that the writer of this communication was using inhalation analgesia and explains very well his technique of administration in the case of labor which he reported. He was adapting to obstetric procedure a method with which he was thoroughly familiar, and that it was carefully planned is further witnessed by the deliberate suspension of anesthesia in order to study the effect on the force of the uterine contractions. This contribution to anesthesia in obstetrics was an important landmark in the history of that subject.

The career of Keep in the development of dental surgery in America was one of outstanding achievement. To him the Harvard Dental School owes its existence, for through his influence the school was established as an integral part of Harvard University, the first association of its kind in the United States. Nathan Cooley Keep was born at Longmeadow, Mass., on Dec. 23, 1800. He attended the village schools and at the age of 16 he was apprenticed to John Taylor, a manufacturing jeweler in Newark, New Jersey. He served an apprenticeship of five years during which time he became interested in dentistry. In 1821 he entered the Harvard Medical School and graduated in the class of 1827 with the degree of M.D. For the next forty years he

maintained. However, to denominate a hospital as a safe or an unsafe place for the handling of obstetric cases merely on the basis that it falls above or below the arbitrary standard of 150 deliveries in a given year is, on the face of it, absurd. All obstetricians whose experience extends to a number of smaller hospitals know that there are institutions in which the volume of work far exceeds this minimum figure in which the standards are woefully inadequate. They also know that there is an occasional hospital of this size, or slightly larger, which is meeting the requirements and rendering commendable service while being economically self-sufficient. On the other hand there are two types of institution that can give good service with less than the specified volume of work. Some small maternity hospitals that abide by the restriction inherent in their name, are well managed on a very low occupancy, and institutions that are endowed, or are willing and able to foot a temporary loss in order to give adequate service are, in a few instances, meeting the requirements with a volume of less than 150 deliveries a year. But, in general, it is safe to say that there are very few general hospitals with less than this minimum whose service to their clientele is adequate.

In order to make a statistical study some point of division had to be made, and, for the reasons given, the figure of 150 deliveries a year was chosen for the purposes of this study. The republication of a table from "An Obstetrical Audit"¹ which was the result of a study made with the help of the vital statistics department of the Ohio Board of Health will help justify the selection made (Table I).

TABLE I. PUERPERAL MORTALITY IN OHIO HOSPITALS

		NO. OF HOS- PITALS	BIRTHS	PUER- PERAL DEATHS	PUER- PERAL RATE
Hospitals approved					
For residencies	1937	17	19,169	119	6.22
	1938	22	25,401	109	4.29
For internships only	1937	22	14,777	98	6.65
	1938	21	14,374	68	4.74
Hospitals not approved for graduate train- ing					
Having more than 150 births a year	1937	40	12,898	119	9.23
	1938	45	14,380	107	7.45
Having less than 150 births a year	1937	66	4,304	78	18.10
	1938	73	3,886	73	18.80

These figures, which are but an expression of the opinion of many experienced obstetricians, prove beyond peradventure the inadequacy of the small hospital from an obstetric point of view. Instances could be cited, such as that of a hospital having 66 deliveries in one year during which there were 3 deaths following cesarean section and one following sepsis, but the figures in the table carry the point without elaboration.

In order to determine the extent of the problem which hospitals having less than 150 deliveries a year present, the following figures have been compiled from the 1938 reports of the Council on Medical Education and Hospitals of the American Medical Association.^{6,7} For the purposes of this study hospitals have been divided into five groups: (1) those having an average occupancy of about 200, which are listed as having over 7,000 admissions a year; (2) those having an average occupancy of between 100 and 200, listed as 3,500 to 7,000 admissions a year; (3) those having an average occupancy of from 50 to 100, listed as 1,750 to 3,500 admissions a year; (4) those having an average occupancy of from 25 to 50, listed as 875 to 1,750 admissions a year; and (5) smaller hospitals, listed as under 875

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

THE SMALL HOSPITAL AS AN OBSTETRIC HAZARD

SCOTT C. RUNNELS, M.D., CLEVELAND, O.

SUBSEQUENT to the recent publication of a study of obstetric results,¹ J. B. DeLee² was one of those who raised the question as to the number of general hospitals in the United States in which obstetrics was being practiced and in which the patient's protection was not adequate. It is in an attempt to make a partial answer to such questions that this study was undertaken.

The report of the committee of the American Hospital Association under the chairmanship of Dr. Buerki,³ the report of the American College of Surgeons,⁴ and the standards adopted by the Hospital Obstetric Society of Ohio,⁵ have clearly defined the requirements that should be met by any general hospital undertaking the care of obstetrics. Briefly stated these are:

A. Obstetrics must be handled in a portion of the hospital completely separated from that devoted to the care of other patients.

B. The personnel handling the obstetric case, particularly the nurses, must have no part in the care of other patients.

C. The hospital must be responsible for supervising the care the obstetric patient receives, ensuring adequate professional treatment.

In order to carry out these provisions, it is necessary that the nursing department of any hospital handling obstetrics shall have a trained obstetric supervisor with a sufficient number of nurse assistants so that they can handle the obstetric work without calling for help from other parts of the hospital. To fully meet this requirement places a serious economic problem on the smaller hospital. However, not to come up to this standard leaves the institution an unsafe place for obstetric care.

During 1936 and 1937 committees of the Hospital Obstetric Society of Ohio visited practically every hospital in the State having as many as 100 deliveries a year. The report of the chairman, Dr. S. R. Burlage, was presented at a joint meeting of the Ohio Hospital Association and the Hospital Obstetric Society of Ohio at Columbus, in April, 1937. This report was approved, and endorsed by both organizations. The following is quoted from this report: "For safe obstetrics there can be but one standard, regardless of the type of institution in which the work is carried on. In the obstetric division of any general hospital, regardless of size, absolute isolation of the division must be practiced. Physical isolation is not enough. There must be separate personnel, without interchange of person, laundry, or equipment; it must be a separate division in fact as well as in name. Any general hospital regardless of size must meet these demands to be authorized as a fit institution to be licensed to handle obstetric patients."

Let us consider what this standard requires of the small hospital. The minimum under which these nursing requirements could be met is to have one nurse on duty in the division with two nurses off duty, at least one of whom could always be called in an emergency. The volume of work necessary to employ one nurse would be at least four cases. The minimum hospital should, therefore, average an occupancy of four obstetric cases. If patients stay an average period of ten days this would mean slightly over 12 births a month or roughly 150 births a year.

This figure of 150 births a year has, therefore, been arbitrarily selected as the minimum number of deliveries with which proper obstetric standards can be

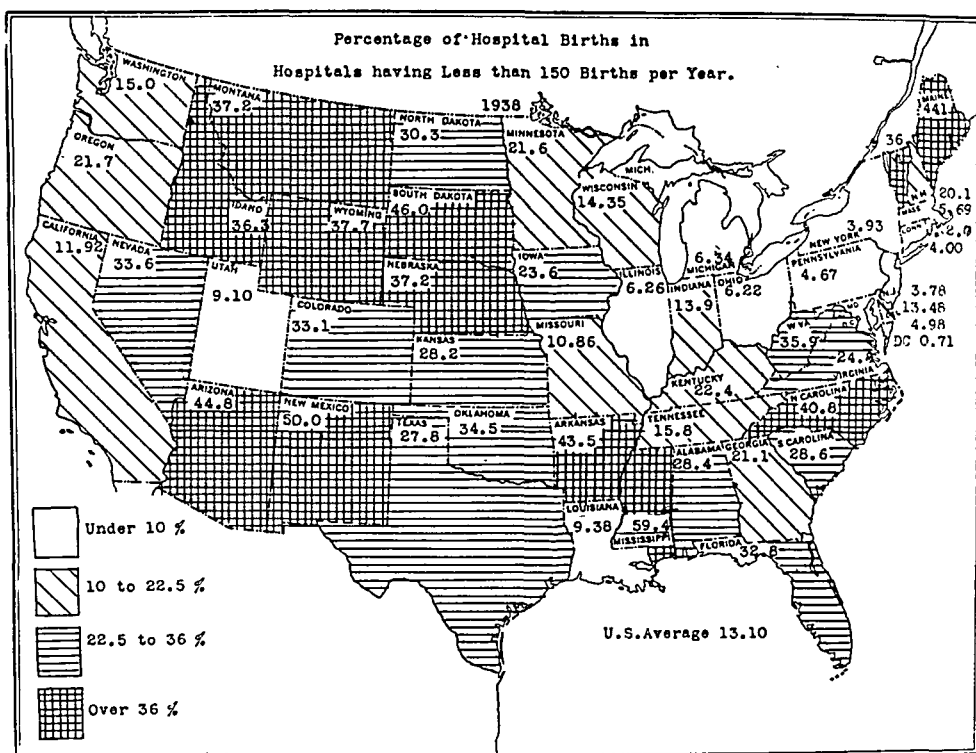


Fig. 1.

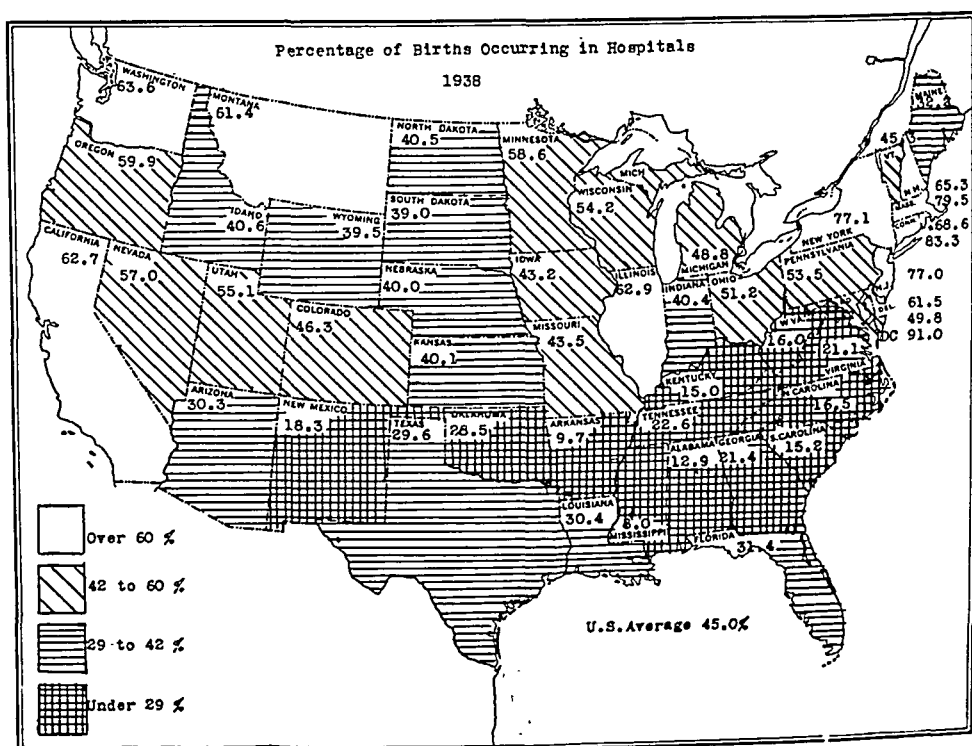


Fig. 2.

admissions a year. Each of these groups was then divided into those hospitals that had over 150 deliveries a year and those hospitals that had less than 150 deliveries a year.

In the two groups of hospitals having an average occupancy of over 100, the number of hospitals having less than 150 births a year, and the number of births occurring in them are very small. In the group having from 50 to 100 average occupancy, there is an increase in the number of hospitals with less than 150 births a year. In the group of hospitals having an average occupancy of between 25 and 50, the number of deliveries in hospitals with under 150 births a year reaches 24.5 per cent of the births in this group. And in the group of hospitals with an average occupancy of under 25, the births in hospitals having under 150 births a year reached 77.0 per cent of all the births occurring in that group. In this group of smallest hospitals there are 84 classified as "Maternity" hospitals, although not all of these restrict their work rigidly to obstetrics. Twenty-nine of these "Maternity" hospitals had over 150 deliveries, and 55 of them had less in 1938. There were no maternity hospitals in the larger groups of hospitals which had less than 150 deliveries a year. Hence, if we grant that the care in these 55 hospitals was acceptable, which is certainly not true of them all, and subtract this 55 from the total hospitals that did not have 150 deliveries, we are left with a total of 2,241 hospitals in which it is difficult to conceive that adequate obstetric care would have been possible. These 2,241 hospitals comprise over one-half (55 per cent) of all the hospitals doing obstetrics in the United States, although only 13.1 per cent of hospital deliveries occurred in them. The percentage of births occurring (Fig. 1) in hospitals of the less-than-150-births-a-year class varied from a percentage of 2.07 in Rhode Island to one of 59.3 in Mississippi. The percentage of hospitalization of obstetrics for each state is presented (Fig. 2) for comparison.

The efficiency of a hospital is considerably determined by the character of its house staff, composed of its residents and interns. This is particularly true when it comes to the management of the obstetric case. Aside from the assistance which this staff renders to the attending physician, which is a real aid to him, and therefore, a distinct benefit to the patient, these doctors are the agents of the hospital administration in meeting the third requirement of adequate obstetric management—the responsibility of the hospital for ensuring adequate professional treatment. The director of the obstetric department cannot personally keep constantly informed as to the status of each patient, but the house staff can bring any abnormal case to his attention. The value of any house staff obviously depends upon the type and amount of the training its members have had. A resident who has passed his first year of graduate training, is more to be relied upon than a first year intern. A department having both residents and interns is superior to one having only one type of service, and the most reliable obstetrical house staff is found in the hospital approved for obstetric residencies.

Examining hospitals from this point of view, we find that the two groups of hospitals having less than an average occupancy of 50 contain no institution approved for an obstetric residency and no institution that is approved for both residents (any type) and interns. Only 10 of the 2,687 hospitals in these two groups are approved for any type of graduate training.

In the next group of hospitals, those having an average occupancy of from 50 to 100, out of the 712 hospitals included, 10 are approved for both residents (any type) and interns and 8 for residencies only. In this group of 18 hospitals there are 5 approved for residencies in obstetrics or obstetrics-gynecology, 2 of them being specialized maternities and 2 hospitals for the colored. Five of the 18 hospitals in the group that have approved residencies do not have 150 deliveries a year. Of the total 712 hospitals of this size 127 are approved for internships only. The remaining 567 of these 712 hospitals are not approved for graduate training. In the two groups having an average occupancy of over 100, there are 1,169 hospitals, and in these hospitals 53.1 per cent of all hospital births occur.

3. Hospitals in this grouping are becoming less numerous, but a disproportionately large number of puerperal deaths still occur in such hospitals.
4. The recognition of the hazard inherent to institutions of this type will hasten their elimination and assist in further lowering the obstetric death rate.
5. There are a large number of hospitals with good obstetric organization and the public and professional sentiment is furthering their increase.

REFERENCES

- (1) *Runnels, S. C.*: J. A. M. A. 113: 402, 1939. (2) *De Lee, J. B.*: The 1939 Year Book of Obstetrics and Gynecology, Chicago, 1940, p. 351 (and personal communication). (3) Manual on Obstetrical Practice in Hospitals, Chicago, American Hospital Association. (4) *MacEachern, M. T.*: AM. J. OBST. & GYNEC. 35: 535, 1938. (5) *Skeel, A. J.*: President's Address, Hospital Obstetric Society of Ohio, 1938. (6) Council on Medical Education and Hospitals, J. A. M. A. 112: 909, 1939. (7) Council on Medical Education and Hospitals, J. A. M. A. 113: 757, 1939.

9400 EUCLID AVENUE

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

JOINT MEETING WITH THE OBSTETRICAL SOCIETY OF PHILADELPHIA AND
THE BOSTON OBSTETRICAL SOCIETY, APRIL 9, 1940

The following paper was presented:

Abdominal Pregnancy. Dr. Clifford B. Lull, Philadelphia, Pa. (For original article, see page 194.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF APRIL 1, 1940

The following papers were presented:

Relation of Ovarian Function to Uterine Fibroids. Dr. E. M. Baker.

Ovarian Cyst With Twisted Pedicle. Dr. E. F. Williams.

MEETING OF MAY 15, 1940

The following paper was presented:

The Relation of Vitamin B₁ to the Reproduction Cycle. Correlation Between Vitamin B₁ Content of Diet and Electrocardiographic Findings in 91 Pregnant Women. Drs. Philip Williams, G. C. Griffith, and F. G. Fralin, Philadelphia (by invitation). (For original article, see page 181.)

Only 96 of these hospitals are not approved for some type of graduate training, and only 33 of them having a total of less than 1,000 deliveries, had under 150 births a year in 1938.

In hospitals that have insufficient staff organization to obtain approval for some type of graduate training it is unusual to find an organized obstetric department headed by a responsible chief of service. This situation also holds true in a number of hospitals approved for intern training only and in some hospitals approved for residencies other than obstetrics. Sometimes even when there is a nominal chief of the obstetric service in a hospital having an approved graduate training status, he, with the aid of his trained assistants, is not always given authority by the hospital to supervise the type of obstetric work carried on within its walls. It is obvious, therefore, that with regard to the kind of professional service that a hospital can offer, even taking the house staff only into consideration, the smaller hospital has difficulty in meeting the requirements of the supervisory bodies.

As shown elsewhere,¹ there has been in the last five years a decrease of 14.4 per cent in the number of hospitals having less than 150 births a year and a decrease of 5.5 per cent in the total births occurring in such institutions. But in spite of this reduction, this study reveals that the small hospital is still a significant factor in United States obstetrics.

In communities having sufficient density of population to ensure support of one or more hospitals able and willing to meet the obstetric requirements, the struggle to keep alive an inadequate obstetric department in a smaller hospital is rarely a service to the community. The problem of adequate obstetric hospitalization in the small town community that is often served by a small hospital is not an easy one. There are a few such small city hospitals in Ohio that have given careful thought to the problem. In each instance there is only one hospital in the vicinity, and it is too small to maintain a properly organized obstetric department. Their answer is home deliveries whenever the obstetric case is normal, but if an abnormal case presents, where surgery or major procedure is needed, that patient is admitted. The result is that comparatively few obstetric cases enter the hospital, seldom more than one at a time, and the contagion, if any, can be thoroughly eliminated before the next case is admitted. There is no risk of cross infection and yet the patient that badly needs hospital care is provided for. This is by no means an adequate solution of the problem, but in view of the lack of proper hospital facilities it is a workable makeshift.

It would be ideal if hospitals could be established in many areas which at present lack such facilities. But this would necessitate not only sufficient funds to build and equip these hospitals, but an adequate endowment to enable them to operate properly until the volume of business could carry the overhead. Further, these hospitals should be adequately staffed, not only with sufficiently trained nursing personnel, but with obstetricians of training. One of the chief reasons that the record of many small hospitals is poor is that the doctors available have not had sufficient experience in the varieties of obstetric complications and lack the breadth of view necessary for balanced judgment. If doctors of proper caliber were available, having at their disposal an adequate hospital plant, they would in all probability soon develop sufficient clientele to maintain the installation. It is difficult for such an ideal situation to develop spontaneously, but if such organizations were established and maintained for a time, they should prove practical in well-selected communities.

SUMMARY AND CONCLUSIONS

1. The hospital with less than 150 births a year is rarely maintained with the proper obstetric safeguards and is usually a hazard to the woman in childbirth.

2. Over one-half of the general hospitals in the United States are in this class and 13.10 per cent of all babies delivered in hospitals are delivered in hospitals of this type.

and Gregg. There seems to be no choice among the various hormonal preparations used; all yield equally unreliable results.

WILLIAM C. HENSKE.

Laves, W.: The Hogben Test for the Biologic Determination of Pregnancy, *Deutsche med. Wchnschr.* 66: 5, 1940.

Laves discusses the technique of the Hogben test and describes the habits, care, and feeding of the African clawfrog *Xenopus laevis Daudini* which responds to the injection of gonadotropic hormone with ovulation. A morning specimen of urine of specific gravity 1.020 or greater is used. This is acidified if necessary to a pH of 5.5 and 1 or 2 c.c. is injected in the frog's dorsal lymph sac. The frog is then placed on a raised large-screen platform an inch or so above the floor of its glass cage. The reaction is generally determined in twenty-four hours. Absence of eggs gives a negative test, 20 to 50 eggs a weak positive, and 50 eggs or more give a positive test.

The findings in a case of adnexal inflammation mistaken for ectopic pregnancy and in a case of pregnancy of less than one month's duration are given.

R. J. WEISSMAN.

D'Erchia, F.: Another Anatomical Report in Favor of Endouterine Nidation of the Human Ovum, *Riv. ital. di ginec.* 20: 463, 1938.

Based on a study of a case of placenta succenturiata, the author affirms that its development occurred upon the decidua reflexa but not upon the decidua serotina, which is deprived of function, less vascular and contains less mucosal glands than the decidua reflexa.

These findings confirm his opinion expressed in a previous paper that the incubating chamber of the human ovum must be considered not as an intradecidual space but as the integral part of the uterine cavity.

AUGUST F. DARO.

Gorman, William A., and Hirsheimer, A.: A Study of the Superficial Venous Pattern in Pregnant and Non-Pregnant Women by Infra-Red Photography, *Surg. Gynec. Obst.* 68: 54, 1939.

The regions photographed by means of infrared rays were the trunk anteriorly and posteriorly and, in a few cases, laterally, and the lower extremities anteriorly and posteriorly.

The following observations were made: No changes occurred in the superficial veins of nonpregnant women during the menstrual cycle. There were no demonstrable differences between the changes in the venous patterns of normal pregnant women and those of pregnant women with organic heart disease or toxemia.

There is an increase in the prominence of the veins of the breasts early in pregnancy, noticeable at the third week, and very definite at the eighth week. At the time of the first noticeable increase in the veins, there is also a noticeable increase in the size of the breasts.

There is an increased prominence of the abdominal venous pattern first noticeable at about the fifth month when there is obvious enlargement of the abdomen.

It is not possible to state from the appearance of the veins whether or not the subject is a primigravida or a multigravida.

Definite changes are limited to the venous pattern of the anterior trunk. There is a marked dissimilarity of venous patterns among all the subjects photographed.

The changes in the prominence of the veins are principally due to the stretching and thinning of the overlying tissues. It is probable that an increase in blood content, and in the case of the breasts, of physiologic hyperemia contribute to the effect.

WILLIAM C. HENSKE.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Physiology of Pregnancy

Martzy, St., and Pap, K.: The Pregnancy Test of Nito, Klin. Wchnschr. 17: 1084, 1938.

Nito recently described a new test for pregnancy for which results were claimed better than those with the Friedman test. Nito found that the injection of urine from pregnant women into the circulation of rabbits produced a marked and rapid leucopenia. Urine from nonpregnant women produced practically no change in leucocyte count.

The authors compared this test with the Friedman test in a series of 150 patients and found the test completely unsatisfactory and unreliable, there being a large percentage of false positives in conditions other than pregnancy. In addition, there were 9 negative tests among 30 early pregnancies and 3 negatives in 18 late pregnancies. The authors therefore conclude that the test should be discarded.

RALPH A. REIS.

Chesley, Leon C., and Chesley, Elizabeth R.: The Cold Pressor Test in Pregnancy, Surg. Gynec. Obst. 69: 436, 1939.

Hines and Brown have proposed the "cold pressor test" which measures the response of the blood pressure to the immersion of one hand in ice water.

Many writers believe that the toxemias of pregnancy, exclusive of true nephritis, are related to primary hypertension. Corwin and Herrick "incline to the view that the subacute, hypertensive toxemia of pregnancy is the response of the woman with latent or declared cardiovascular disease to the strain of pregnancy." If the cold pressor test enables one to pick out the patients with latent or potential cardiovascular disease, as Hines and Brown believe, then perhaps it would also enable one to detect patients likely to develop toxemia of pregnancy. This would be of great importance for the study of toxemia and might even be of some benefit to the patient.

In the present investigation, cold tests have been done in the third or early fourth month, again in the eighth or early ninth month and again six weeks or more post partum in 517 women.

The response to the cold test is inconstant. While many patients do give reproducible rises in blood pressure, others have given highly variable responses at different times.

The response to the cold test is independent of family history of cardiovascular-renal disease and diabetes. It is also independent of age, gravidity, weight, weight-height index, weight gain in pregnancy, and perhaps also the basal blood pressure.

The incidence of toxemia is essentially the same in both normal and hyperreacting groups. The frequency distribution of responses is essentially the same in both pretoxemic and "prenormal" groups.

WILLIAM C. HENSKE.

Parsons, Susanne R.: Evaluation of the Intradermal Test for Pregnancy, Surg. Gynec. Obst. 68: 187, 1939.

The intradermal skin test for pregnancy in 679 cases has proved entirely unreliable in the hands of all workers who have attempted to repeat the work of Gilfillen

It was found that the erythrocyte counts and hemoglobin estimations for pregnant women are 10 to 15 per cent lower than for healthy nonpregnant women of the same age group. The hemoglobin and akaryocyte (nonnucleated erythrocyte) counts for the sternal marrow in pregnancy are somewhat lower than the corresponding counts for the blood. The leucocyte counts of the blood during pregnancy are significantly higher than for healthy nonpregnant women. The total nucleated cell counts for the marrow are definitely higher in pregnant than in nonpregnant women. It is noteworthy that there is no decrease in any of the nucleated erythrocytes during pregnancy, which indicates that the physiologic anemia of pregnancy is due not to decreased erythrocyte production but, as others have shown, to the increase in plasma volume. There is even a slight increase in the reticulocyte counts during pregnancy, suggesting that there may be a slightly increased rate of erythrocyte formation.

J. P. GREENHILL.

Cetroni, M. B.: Fetal and Maternal Polypeptidemia, *Riv. ital. di ginec.* 22: 429, 1939.

By the method of Cristol and Puech, the author determined the polypeptidic azote contents in blood serum of 18 healthy, nonpregnant women (average mg. 2.88 per cent) and of 48 pregnant women from the fourth month to full term.

He observed a progressive increase of polypeptides during pregnancy (average mg. 3.66 per cent up to fourth, fifth and sixth months; mg. 4.17 up to seventh and eighth months; mg. 4.85 per cent up to ninth month and at term).

Researches at the same time carried out for the fetus showed that the level of polypeptides in the fetal blood serum is always higher than the maternal, averaging: mg. 3.87 per cent for the fetus up to fourth, fifth, and sixth months; mg. 4.49 per cent up to the seventh and eighth months; and mg. 5.81 per cent up to the ninth month and at term.

The polypeptidic azote in the blood serum of the umbilical vein is always higher than that in the blood serum of the umbilical arteries (respectively, mg. 6.14 and mg. 4.92 per cent).

The fetal polypeptidemia is higher than the maternal, because in the cord blood are not only the polypeptides of the maternal blood but also those that originate from the action of proteolytic placental ferments.

The higher contents of polypeptides in the blood of the umbilical vein as compared with the arteries might be a proof of the utilization by the fetus of the polypeptides that are derived from the placenta, and might indicate action of the fetal liver in the synthesis of the azoted substances.

In the blood of the newborn child the level of the polypeptides diminishes rapidly. This is probably due to the sudden suspension of transplacental passage of polypeptides.

AUGUST F. DARO.

Quinto, Pietro: Phosphatase During the Puerperium, *Riv. ital. di ginec.* 22: 347, 1939.

The author studied with the method of Jenner and Kay the behavior of the plasma's phosphatase contents during the various periods of pregnancy, labor and puerperium. He found that in pregnancy phosphatase increases progressively until it reaches the maximum values during the last month and in labor, after which it returns to the normal level within the first ten days of the puerperium.

The author determined that the phosphatase contents of the fetal blood at the time of birth are relatively high but always less than those of the mother's blood.

AUGUST F. DARO.

Elmby and Christensen: Ascorbutic Acid in Pregnancy, Labor, the Puerperium and the Neonatal Period, *Klin. Wehnschr.* 17: 1432, 1938.

The authors' studies were carried out in 500 women during the last five months of pregnancy, during labor, and throughout the puerperium. Determinations were

Patat, P.: Relations Between Ocular Tension and Pregnancy, Zentralbl. f. Gynäk. 62: 868, 1938.

Comparative tests on nonpregnant women of the same age revealed that the ocular tension of pregnant, parturient, and puerperal women is usually reduced. In 27 women in whom the values had been found definitely reduced during pregnancy, the author renewed the test one or two years after delivery. The presented tabulation clearly demonstrates that the ocular tension of the same person is usually lower during the processes of gestation than is the case one or two years after delivery. Discussing the possible cause of the ocular hypotension during pregnancy, the author suggests first that the acidosis of pregnancy might play a part, pointing out that a lowered ocular tension has been observed during other processes that are accompanied by acidosis, such as diabetic coma. Other factors that might be involved are reduction in the osmotic pressure, chemical changes in the blood, or changes in the endocrine function. A complete explanation has not been found as yet.

J. P. GREENHILL.

VanLiere and Sleeth: The Question of Cardiac Hypertrophy During Pregnancy, Am. J. Physiol. 122: 34, 1938.

On the basis of their investigations on guinea pigs, cats and dogs, the authors maintain that pregnancy does not cause cardiac hypertrophy in these animals. Since pregnancy does not produce cardiac hypertrophy in three different types of animals, it seems doubtful that it would produce it in human beings. Increased cardiac work does not necessarily produce cardiac hypertrophy.

J. P. GREENHILL.

Bortolucci, P.: The Detoxicating Function of the Liver During the Puerperal State, Riv. ital. di ginec. 20: 445, 1938.

Using santonine as an hepatic toxic agent to test the detoxicating function of the liver of pregnant women, the author concludes that pregnancy acts to reduce the antitoxic quality of liver function.

AUGUST F. DARO.

Ramsay, Thierens, and Magee: The Composition of the Blood in Pregnancy, British M. J. 1: 1199, 1938.

The hemoglobin, the bactericidal power of the blood against hemolytic streptococci, and the calcium, inorganic phosphorus, and phosphatase contents of the serum were studied in 101 women at the seventh month of pregnancy.

Seven per cent were found to be definitely anemic and 19 per cent probably slightly so. In 39 per cent, the calcium level was less than 9 mg. per 100 ml., which is believed to be abnormally low. The product calcium \times phosphorus was 25 on the average. The blood of 22 patients failed to inhibit the growth of streptococci and, of these, one developed pyrexia during the puerperium; fever also occurred in a patient whose blood inhibited growth at the seventh month.

The literature reveals that the serum calcium and phosphorus fall and the serum phosphates rise gradually as gestation advances.

F. L. ADAIR AND S. A. PEARL.

Pitts and Packham: Hematology of Sternal Marrow and Venous Blood of Pregnant and of Nonpregnant Women, Arch. Int. Med. 64: 471, 1939.

Of 40 pregnant women attending the outpatient maternity clinic of the Vancouver General Hospital none had a past history suggesting a blood dyscrasia, and all of them were found by consideration of the history and by physical examination to be in good health. For comparison, studies were made on 24 healthy nonpregnant women of about the same age.

Valentinuzzi, Maximo: The Physics of the Gravid Uterus: Its Pressure, Tension, Tone, Contractions, and Labor, *Rev. méd. latino-am.* 284: 290, 1939.

Summarizing his studies the author states that mathematical analysis of forces that participate in the uterine mechanism of labor permits to establish some quantitative relations between myometrium shortening and intrauterine pressure (Weber-Wolf's law), between tension of the uterine wall and intrauterine pressure (Barrau-De Snoo's law), between myometrium shortening and uterine tension, between amplitude of the contraction and uterine tension, and between expulsive work and intrauterine pressure. All of these relations offer one further step toward a rational systematization of the knowledge about the uterus during labor. The electrical theory of muscular activity introduces the concept that tone and contraction depend on the same physical mechanism, that is, on electrical charges, so that it seems correct to state that *tone is a function of contractility*. This interpretation does not deny the experimental facts which characterize tone and contraction, but they are included and explained in it. The variation of the uterine muscular tension, either as tone or as contraction when the other factors remain unchanged, depends on a change in the intramuscular charges produced by physiologic (hormonal, biochemical, nervous) or pharmacologic stimuli. In this sense, oxytocic substances would elevate the electrical charge of the myometrium and sedative substances would diminish it.

MARIO A. CASTALLO.

Siegler, S. L.: Estrogenic and Chorionic Gonadotropic Hormone in Pregnancy, *J. Lab. & Clin. Med.* 24: 1277, 1939.

In an interesting report, Siegler compares the urinary estrogen and chorionic gonadotropin in five normal and one toxemic pregnancies. Findings in the case of toxemia at sixth or seventh month of pregnancy indicated the presence of an excessive amount of anterior pituitary-like substance, with a concomitant decrease of total estrogen to term. Twelve days before confinement the urine contained 31,700 R.U. estrogen and 49,000 M.U. of gonadotropic hormone. The patient had hydramnios, generalized edema, severe headache, epigastric distress, and nausea; 1,000,000 I.U. of estradiol benzoate were given over the following ten days, with subsidence of symptoms and a change in the urinary endocrine picture to 52,000 R.U. estrogen and 12,000 M.U. gonadotropic hormone.

Five normal cases showed an average increase of estrogen from 3,500 R.U. thirty days after the first missed period to a peak of 82,000 R.U. at term. Gonadotropic hormone normally rose from 7,500 M.U. on the fourteenth day after the first missed period to 40,000 M.U. on the thirtieth day, with a rapid decline to levels of 10,000 M.U. decreasing evenly to 4,500 M.U. at term, and being absent four days post partum.

The author found that serum concentrations of hormones coincided with their concentration in the urine. He feels that the variations found in toxemia may possibly be the result of the visceral lesions found clinically in eclampsia and pre-eclampsia.

R. J. WEISSMAN.

Lubin, Samuel, and Waltman, Richard: Results of Attempted Induction of Labor with Estrin, *Surg. Gynec. Obst.* 69: 155, 1939.

Estrin can initiate and maintain uterine motility and contractility in animals and human beings. Experimental evidence has been cited to show that pregnancy in certain animals can be terminated by estrin administration.

The reports of successfully induced labor by estrin in the human being are inconclusive, because in practically all instances estrin was employed along with other procedures or substances which might in themselves produce labor.

The authors attempted to induce labor near, at, and beyond term by administration of estrin without additional aid. Of 36 patients employed in the investigation, it is possible that the onset of labor could be attributed to the injected estrin in 8 cases. It is also possible that the estrin might have been responsible for the

made of the acid content of the blood, urine, milk as well as of the umbilical cord blood and blood from the ear of the newborn infant. A direct relation was found between the acid intake and the acid level of the blood, and of the milk. The levels found during the latter half of pregnancy were definitely below those of the non-pregnant. The acid level of the newborn infant approximates that of the mother and is dependent upon it. The level sinks rapidly during the first ten days of life. Increasing the oral intake during the puerperium will maintain serum and milk levels at the normal nonpregnant level. The authors conclude that the usual winter rations of Germany are markedly deficient in vitamin C.

RALPH A. REIS.

Grossi, Giuseppe: Relation Between the Elimination of Ascorbutic Acid in the Urine and Interruption of Pregnancy, *Folia dermatograph. gynaece.* 36: 328, 1939.

The author studied the excretion of vitamin C in its relationship to pregnancy in a group of patients, particularly concerning probable interruption of pregnancy.

It seems that in patients with threatened abortion, ascorbutic acid content is lowered in the urine. The author studied in all 32 cases where the threatened interruption did not terminate in abortion and seven patients in whom the threatened interruption continued to abortion.

In the first group the average ascorbutic acid content of the urine was 4.7 mg. per 100 c.c. while in the latter group this content averaged 2.3 mg. per 100 c.c. He found that in normal pregnancy the average ascorbutic acid content of the urine was 4.1 mg. per 100 c.c.

MARIO A. CASTALLO.

Sadovsky, A., Weber, D., and Wertheimer, E.: Concentration of Vitamin C in Blood During and After Pregnancy, *J. Lab. & Clin. Med.* 25: 120, 1939.

Determinations of vitamin C in the blood were made immediately upon withdrawal of the blood in 222 women. The average concentration was 1.01 mg. per cent. There were several interesting findings. The vitamin C concentration was highest during pregnancy; lowest after confinement. The highest values were found during the citrus fruit season. During hyperemesis gravidarum, a secondary decrease in vitamin C was noted, but substitutive administration of the vitamin in one case had little effect on the hyperemesis.

R. J. WEISSMAN.

Nixon, J. A.: Diet in Pregnancy, *Bristol Med.-Chir. J.* 56: 165, 1939.

Discussing dietary influences on gestation, Nixon concludes that much more investigation must be done on the effects of modifying the diets of expectant mothers. Well-fed mothers appear to be less liable to puerperal sepsis. In 48,881 cases studied by the Joint Council of Midwifery, the infant mortality (stillbirths plus neonatal) per thousand was 59 for mothers receiving special foods, puerperal sepsis accounting for 0.26 mothers per thousand. Mothers not receiving special foods, but attending antenatal clinics, had an infant mortality rate of 71; sepsis deaths 0.67 per thousand. Those not attending clinics and not obtaining special foods had an infant mortality of 92; sepsis deaths 0.88 per thousand.

The importance of the various elements of the diet is discussed in detail. The average caloric requirement of an active nonpregnant woman is given as 2,500 calories per day. In pregnancy this should be gradually increased after the fourth month to a 20 per cent increase over the above figure. The League of Nations Technical Commission recommends a diet yielding 3,440 calories and gives the daily requirements of protein, 105 Gm.; calcium, 1.6 Gm.; phosphorus, 2.0 Gm.; iron, 10.2 mg.

R. J. WEISSMAN.

Announcement

The October issue of the JOURNAL will commemorate the twentieth anniversary of its establishment as an organ of publication in the domain of American obstetrics and gynecology. This special issue will present a series of brief, critical articles by a selected group of contributors, based on the developments during these past two decades in the fields to which the JOURNAL has been devoted.

We bespeak the attention of our readers to this anniversary number.

Item

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 5, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, immediately prior to the 1941 meeting of the American Medical Association.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pennsylvania.

short labors in 4 of the 9 primiparas in this series. The onset of labor bore no relationship to the dosage of estrin employed.

The findings merely suggest the possibility that labor in the human being near, at, and beyond term might be induced by estrin administration and that duration of labor might be shortened by this method.

WILLIAM C. HENSKE.

Wiessman, A.: Calculation of the Duration of Pregnancy, *Klin. Wehnschr.* 17: 1611, 1938.

The author studied the duration of pregnancy in 5,000 consecutive deliveries and the relation of this duration to the type of menstrual cycle. It was found that the average duration of pregnancy was 280 days. Furthermore there was no demonstrable relation to the type of menstrual cycle, since the length of pregnancy was the same whether the pregnancy was in a woman with a 26-, 28-, or 35-day cycle. The author sees no reason to discard the Naegele rule for calculating from the first day of the last menstrual cycle by subtracting three months and adding eight days. He proves that the method is most accurate.

RALPH A. REIS.

Kreis, J.: Prolonged Pregnancy or Late Fecundation, *Rev. franc. de gynéc. et d'obst.* 33: 120, 1938.

Kreis believes that the normal duration of pregnancy in women who menstruate every twenty-eight days is not 280 days but 285 days on an average. In most cases of supposedly long pregnancy, the duration of pregnancy is actually normal but fecundation took place late in the menstrual cycle. That fecundation may take place late in the cycle is evidenced by the fact that ovulation can take place from the eighth to the twenty-seventh day. Hence, in cases where labor is supposedly overdue, we should not be anxious to induce labor.

J. P. GREENHILL.

Bernhart, F.: The Duration of Pregnancy and Its Seasonal Influences, *Monatschr. f. Geburtsh. u. Gynäk.* 107: 215, 1938.

The author studied 4,000 labor cases and came to the conclusion that the season of the year plays a role in the duration of pregnancy. He found that there was a slight increase in the number of prolonged pregnancies in summer and also a diminution in the number of short pregnancies during this time. However because of the small number of cases, no decisive conclusions can be drawn.

J. P. GREENHILL.

Books Received

AN INTRODUCTION TO MEDICAL MYCOLOGY. By George M. Lewis, M.D., associate and assistant attending dermatologist, New York Post-Graduate Medical School, Columbia University, etc., and Mary E. Hopper, M.S., assistant in mycology, Skin and Cancer Unit, New York Post-Graduate School. 315 pages, 71 figures. The Year Book Publishers, Inc., Chicago, Ill., 1940.

EL DIAGNOSTICO PRECOZ DEL EMBARAZO. Par Dr. Carlos Colmeiro Laforet. 244 pages, illustrated. Libreria "Gali," Santiago de Compostela, 1940.

TEXTBOOK OF HISTOLOGY. By Harvey Ernest Jordan, professor of anatomy and director of anatomical laboratories, University of Virginia. Eighth edition, 690 pages, 609 illustrations. D. Appleton-Century Co. Inc., New York, 1940.

In the past twenty-five years, certain clinical observations have influenced the attitude of obstetricians and gynecologists as to the importance of retrodisplacement of the uterus as a clinical entity. Within this time we have acquired more exact knowledge of the relationship of retroversion to sterility. Obstetricians have become less concerned regarding the progress of pregnancy in a retroverted uterus and have found that under such circumstances the use of the pessary is rarely indicated. Realization of the fact that a high incidence of congenital backward displacements of the uterus occurs in all classes of women, has influenced many gynecologists and obstetricians, perhaps unwisely, to disregard symptomless postabortal and post-partum retroversion. Sampson's classic studies on endometriosis have aroused the interest of gynecologists in the possibility that retroversion, especially when associated with stenosis of the cervical canal, may favor the development of this serious condition. Follow-up studies have compelled gynecologists to be more careful in their selection of patients for whom relief of symptoms by surgical means seems indicated. To avoid the embarrassment of failing to cure preoperative symptoms and especially backache, more patients are being subjected to routine orthopedic examinations and therapeutic tests with retroversion pessaries to be sure that the backache and other symptoms of which they complain are really gynecologic in origin.

Finally, after extensive clinical experience, some gynecologists are doubtful as to whether retrodisplacement of the uterus, of itself, is ever responsible for physical symptoms. They are convinced that symptoms usually attributed to retroversion are almost invariably due to commonly associated functional and pathologic conditions of the cervix and uterine adnexa.

In relation to pregnancy, retrodisplacement of the uterus and the conditions associated with it present a threefold problem, because together they constitute an important etiologic factor in the causation of sterility, a common cause of abortion and conditions frequently responsible for unpleasant postabortal and post-partum symptoms. From a study of the relationship of retroversion and its associated conditions to pregnancy, it seems certain that the same underlying disturbances of function may be responsible for either sterility or early abortion.

Authorities are agreed that in the examination of women who seek advice on account of sterility, approximately 10 per cent will be found to have backward displacements of the uterus.

In the past it was believed that some women who had uncomplicated retroversion, were sterile because the cervix was turned forward out of the pool of semen and that for this reason proper insemination failed to occur. It is still considered that fertilization is more likely to occur if the development and position of the cervix are such that ejaculation of semen is directed into the external os of the cervical canal.

Comparatively recent observations, especially those in the field of endocrinology, have served to focus our attention on other important causes of sterility and early abortion. As a result of these observations,

American Journal of Obstetrics and Gynecology

VOL. 40

SEPTEMBER, 1940

No. 3

Announcement

The October issue of the JOURNAL will commemorate the twentieth anniversary of its establishment as an organ of publication in the domain of American obstetrics and gynecology. This special issue will present a series of brief, critical articles by a selected group of contributors, based on the developments during these past two decades in the fields to which the JOURNAL has been devoted.

We bespeak the attention of our readers to this anniversary number.

Original Communications

RETRODISPLACEMENT OF THE UTERUS IN RELATION TO PREGNANCY*

WITH SPECIAL REFERENCE TO THE TECHNIQUE AND END RESULTS OF
THE BISSELL OPERATION

ALBERT H. ALDRIDGE, B.S., M.D., F.A.C.S., NEW YORK, N. Y.
(*From the Clinic of the Woman's Hospital*)

IN VIEW of all that has been written regarding the management of retrodisplacement of the uterus, one feels rather compelled to justify an effort to arouse the interest of gynecologists to reconsider the success and logic of accepted methods of treatment. If there is any justification for further discussion of this subject it is because:

1. Retroversion of the uterus will probably always be one of the more common gynecologic conditions requiring treatment and surgical intervention for the cure of symptoms in some cases.

2. Differences of opinion still exist as to indications for treatment of retroversion by both palliative and surgical means.

3. Follow-up records show that every retroversion operation in use at present, carries with it a definite although perhaps small percentage of surgical failures.

*Read at a meeting of the Chicago Gynecological Society, April 19, 1940.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

and the tubes are found to be normally patent, it is quite probable that a thorough investigation will reveal other causes for a sterile marriage.

For sterile women with retroversion who have definite disturbances of the menstrual cycle and evidence of tubal occlusion or obstruction, active treatment is indicated. Menstrual symptoms may be relieved; tubal patency may be restored and conception may be allowed to occur if the uterus can be held in normal position by a well-fitted retroversion pessary. If the uterus cannot be replaced or if treatment with a pessary fails to give the desired result after a reasonable period of time and the husband has been found to be fertile, treatment of the retroversion by surgical means is usually indicated. At operation peritoneal adhesions or other pelvic pathology, which could not be made out by bimanual examination, may be found.

In discussing the conditions responsible for sterility, in relationship to uterine retroversion, attention has been called to certain factors which, under the same circumstances, are believed to predispose to early abortion. There is another small group of cases in which pregnancy in a retroverted uterus may be disturbed by the fact that the uterus fails to spontaneously assume a forward position as pregnancy advances. This is because it is either adherent to the peritoneum of the pelvis or because it becomes incarcerated in the hollow of the sacrum. Under such circumstances, the uterus can usually be dislodged with gentle bimanual manipulation. Occasionally this can best be done with the patient well relaxed under surgical anesthesia. Peritoneal adhesions will usually soften and give way as the uterus enlarges. Rarely is operation necessary to release such adhesions.

In recent years there has been an increasing tendency for many obstetricians to disregard asymptomatic post-partum retroversion. There are probably two important reasons for this change of attitude, namely,

1. Experience has shown that a considerable percentage of such retrodisplacements are either congenital in origin or the result of conditions which have caused chronic retroversion before the onset of pregnancy. It is an accepted fact that under such circumstances, a cure of uterine backward misplacements cannot be effected by palliative means.

2. With the adoption of delivery by prophylactic forceps after perineal incision as an almost routine procedure by many obstetricians, the great majority of women are left with perineal bodies and vaginas which closely approximate the nulliparous state.

Even though an episiotomy wound has healed normally, sufficient distention of the vaginal introitus to allow manual replacement of a retroverted uterus and insertion of one of the retroversion pessaries of the Smith or Hodge type, is usually accompanied by considerable discomfort for at least two to three months after delivery. For this reason obstetricians are reluctant to subject their patients to the discomfort of such treatments unless there are symptoms which cannot otherwise be relieved. They prefer to omit treatment with pessaries in the hope that when involution is complete, nature will have corrected those misplacements which have resulted from conditions associated with the pregnancies recently terminated by various methods of delivery.

the disturbances in function of the pelvic organs which may be associated with retroversion are better understood.

Retrodisplacement of the uterus is invariably accompanied by prolapse of the uterine adnexa, retardation of circulation in the blood vessels of the broad ligaments and some degree of chronic passive congestion of the uterus, tubes, and ovaries. Lacking proper nutrition, ovarian function is impaired. Normal maturation and rupture of some of the Graafian follicles may fail to occur; the ovaries may become cystic and the endometrium is frequently found to be hyperplastic. The common occurrence of menstrual disorders in the presence of chronic retroversion can be readily explained by interference with the process of oogenesis and the inevitable disturbances in ovarian hormone production.

Under such circumstances, it is believed that factors which contribute to the causation of sterility and early abortion are:

1. A reduction in the total number of normal ova produced.
2. Production of imperfect ova which either cannot be fertilized or, if fertilized, are cast off early in pregnancy because they lack qualities necessary for mature development.
3. An abnormal endometrium which predisposes to abortion because proper nidation of the fertilized ovum fails to take place.

In the presence of uncomplicated chronic retroversion, the lumina of the Fallopian tubes are often occluded or obstructed. This may be due to various causes, such as, angulation, thickening of the mucous membrane lining of the tubes as a result of congestion and hyperplasia, adhesions from healed endosalpingitis and plugs of mucus within the lumina.

Furthermore it is believed that the conditions associated with retroversion reduce local resistance of the abdominal pelvic organs to infection. Peritoneal adhesions and tissue damage resulting from healed inflammations add to the incidence of tubal occlusion and obstruction found in the examination of these cases.

In a small series of sterility patients operated upon for uncomplicated retroversion at the Woman's Hospital, 42.8 per cent showed tubal occlusion or obstruction when examined before operation, although the tubes appeared to be normal at time of operation. Rubin¹ reports that "tubal obstructions were met with in 66 per cent of backward displacements" of the uterus.

From all that is known regarding the relationship between uncomplicated retroversion and sterility, it is obvious that the most important objective physical finding is the frequent occurrence of interference with tubal patency. Certainly no sterile woman who has a retroversion can be considered to have been properly examined to determine the cause without having had a test for tubal patency.

It is an accepted fact that many women conceive readily in spite of backward displacements of the uterus. Undoubtedly in these women ovarian function has not been seriously disturbed and the patency of the Fallopian tubes has not been affected by the existing misplacements. When, notwithstanding the retroversion, menstrual periods are normal

The result of any gynecologic operation to be regarded as entirely satisfactory should mean that preoperative symptoms have been relieved, that normal anatomic relationships have been restored and that normal function of the organs or parts involved is to be expected. On this basis it is obvious that surgeons lack confidence in the success of operations being done for retroversion probably because they not infrequently fail to withstand the most important test of function, namely, pregnancy. Otherwise, how can we explain the fact that so many patients that come for the relief of retroversion symptoms have been advised, even by gynecologists, to postpone treatment by surgical means until they no longer anticipate subsequent pregnancies? If a woman accepts this advice it may mean that she must either undergo a prolonged course of gynecologic treatments or endure her symptoms and some degree of physical disability for a number of months or years.

Therefore it would appear that there is still need for an operative technique which will re-establish physiologic function of the structures which support the uterus in a normal anterior position and in a way that is more likely to withstand the conditions associated with pregnancy.

In the annals of gynecologic history, the year 1940 might very well be regarded as the one hundredth anniversary of the development of the first surgical technique for the cure of retroversion. Records show that it was in 1840, exactly 100 years ago, that Alquié³ suggested the first definite plan whereby this condition might be treated by surgical means. Since that time, well over 100 retroversion operations have been devised. The treatment of retroversion is no exception to the rule that, when many techniques are advised for the surgical cure of any condition, none is likely to be uniformly successful as to results.

In recent years, significant changes have occurred in our approach to many gynecologic problems. Routine follow-up studies have demonstrated the necessity for modifications of many accepted gynecologic operative procedures in order to reduce the incidence of unsatisfactory end results. This is particularly true as regards operations for the repair of vaginal birth injuries and those for the cure of uterine prolapse.

If we study the improvements in technique that have been devised, we can hardly fail to realize that they have been made possible through a more exact knowledge of the anatomy and physiology of the pelvic organs and a better understanding of the musculofascial structures which are necessary to support these organs in normal position. For instance it has been found that uniformly satisfactory end results in the cure of vaginal birth injuries cannot be had by working with superficial denudations of vaginal mucous membrane in geometric patterns. No longer is it necessary to interpose the body of the uterus between the bladder and anterior vaginal wall to cure a large cystocele. For the surgical treatment of a prolapsed uterus we no longer depend upon a technique which fixes the fundus to the anterior abdominal wall. Provided there is no justifiable reason for removing such a uterus, the modern acceptable technique to cure the condition is one which aims to

It is probably fair to state that the only circumstances in which retroversion pessaries are useful in preventing chronic retroversion are after abortion and in the post-partum period. By relieving tension on the relaxed musculofascial supports of the uterus, normal involution is allowed to occur and physiologic function of the supporting structures of the uterus is thereby restored. Under all other circumstances, a retroversion pessary acts simply as a splint to hold the uterus in anterior position with the hope that symptoms caused by the condition will be relieved.

If obstetricians fail to take advantage of the most favorable opportunities to treat retroversion, namely, after abortion and in the post-partum period, it is possible that some women may be subjected to the necessity for subsequent gynecologic treatments or operations which might have been avoided.

It seems entirely justifiable to disregard an asymptomatic postabortal or post-partum retroversion if it is known that the uterus was retrodisplaced before the onset of pregnancy. However, many women never submit to pelvic examination until they are six to eight weeks pregnant. It is known that a backward displacement of the uterus, if discovered then, may be due to conditions associated with early pregnancy.

It is an admitted fact that many uteri found misplaced following abortion or delivery will be spontaneously restored to normal position when involution is completed. However, if there is no proof that retroversion preceded pregnancy, it seems wise to institute treatments, such as suitable exercises, vaginal douches and artificial means to support the uterus while involution is in progress. There is evidence to prove that such measures tend to promote proper involution of the pelvic organs and to reduce the incidence of permanent backward displacements.

It may be worth while to call attention to an ingenious pessary devised by Findley.² This pessary is a modification of the Smith type, in which a section of flexible rubber has been vulcanized into both its anterior and posterior margins. By this change in construction, it is possible to fold the pessary so that it may be inserted with no more distention of the vagina than is required for examination with one finger. From experience in the use of this pessary it seems certain that it supports the uterus as well as the one originally devised by Smith.

The most frequent indications for surgical treatment of retroversion will occur in women who have associated functional and pathologic conditions of the pelvic organs causing a variety of symptoms, such as pelvic pain, menstrual disorders, and backache. These symptoms may be caused by chronic passive congestion of the pelvic organs, cystic ovaries, healed inflammatory disease, or neoplasms involving the uterus, tubes, and ovaries.

A great majority of the women requiring such operations are within the childbearing period. Operative procedures to cure the conditions should be selected because they are conservative and because they are the ones best suited to withstand the test of future pregnancies.

It is probably fair to state that general surgeons and most gynecologists regard the surgical treatment of retroversion to be simple, reasonably successful and perhaps settled.

broad ligaments considered an important feature of the technique. In the Coffey operation, the proximal ends of the broad ligaments are incidentally folded over and sutured to the anterior surface of the uterus. With other operations such as Montgomery-Simpson and Webster-Baldy, puckering of some of the tissues of the broad ligaments necessarily occurs as the round ligaments are shortened. This may result in slight increased tension of the broad ligaments when healing is complete.

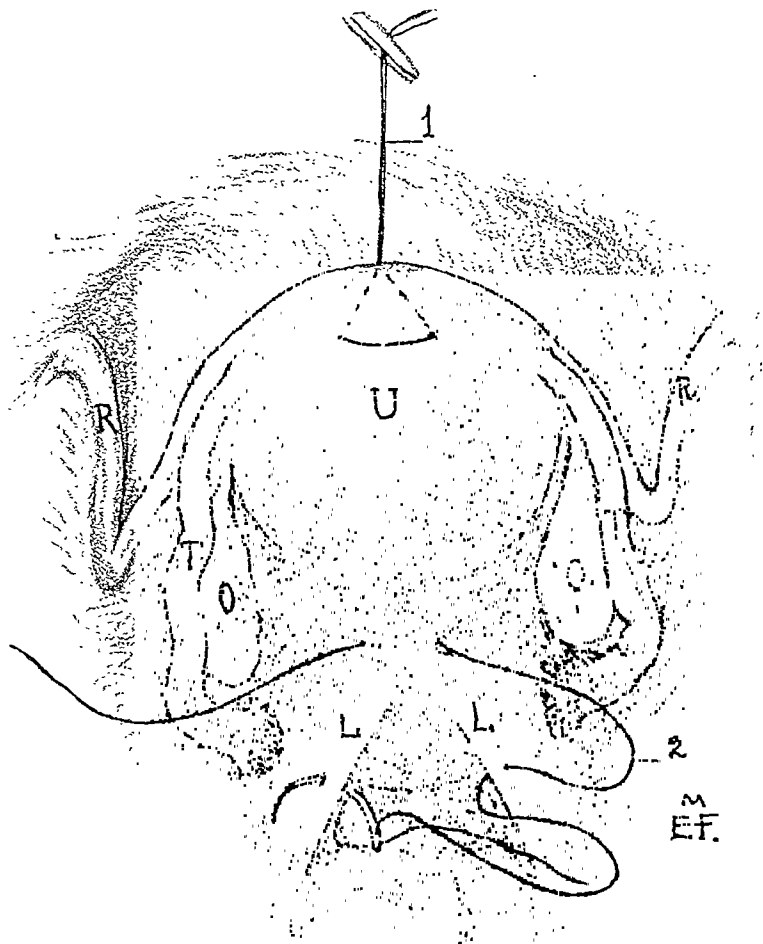


FIG. 1.—Shows the uterus, *U*; tubes, *T*; ovaries, *O*; round ligaments, *R*; and uterosacral ligaments, *L*. The uterus is being pulled forward by a chromic catgut No. 1 suture (1), which is used for traction during the operation and finally as a means of temporarily suspending the uterus to the anterior abdominal wall. Also shows a linen suture (2), which has been passed through the posterior surface of the uterus (*U*), and the uterosacral ligaments (*L*) in accordance with the technique recommended by Noble for shortening these ligaments.

In 1901, the late Dr. Dougall Bissell, attending surgeon at the Woman's Hospital, who was always deeply interested in the character and function of the structures which support the uterus, devised a surgical technique for the cure of retroversion by which both the broad and round ligaments could be shortened. In an article published in 1916,⁴ he described the technique that had been developed and reported his results in 185 patients who had been operated upon. Having followed many of the patients for long periods of time and some through subse-

re-establish its normal supports by repairing the damaged or overstretched so-called cardinal or Mackenrodt's ligaments.

In other words it is obvious that progressive improvement in the results of our gynecologic operative procedures has been accomplished by adopting modifications in technique and new methods which are based upon sound anatomic and physiologic principles.

From a study of the operative techniques which have been recommended for the cure of retrodisplacements of the uterus, by the abdominal route, we can hardly fail to be impressed with the ingenuity of some surgeons who have developed such procedures. In modern times, surgeons attempt to select the technique best suited to the conditions present at time of operation. They almost invariably employ one of five methods which are well known by the names of the surgeons who devised the procedures, namely, Gilliam, Montgomery-Simpson, Webster-Baldy, Coffey and Olshausen. The fundamental principle underlying all of these procedures is some scheme for shortening the relaxed round ligaments. In some instances, these operations are combined with surgical techniques for shortening the uterosacral ligaments and procedures to give additional support to the prolapsed uterine adnexa. In a small percentage of cases, retrodisplacements of the uterus are treated by techniques which permanently fix the fundus to the anterior abdominal wall.

The advantages and disadvantages of all these methods are too familiar to members of this society to require any comment.

From our knowledge of pelvic anatomy, it is known that all the pelvic organs are surrounded and supported by a thin layer of fascia, known as the endopelvic fascia. At the level of the internal os of the cervix, the uterosacral, cardinal, and pubocervical ligaments form a continuous plane of tissue which serves to support the nonpregnant uterus in a normal, more or less constant position as regards its level in the pelvis and the relationship of the cervix to the pubis, sacrum, and lateral walls of the true pelvis. This layer of tissue, often referred to as the upper pelvic floor, is a part of the endopelvic system of fascia.

Backward displacements of the uterus and prolapse of the uterine adnexa are prevented by normal function of the round and broad ligaments. The round ligaments are composed essentially of smooth muscle and the broad ligaments contain two layers of fascia derived from the endopelvic fascial system.

The frequent occurrence of congenital retroversion is often attributed to the fact that, through the processes of evolution, women have acquired an upright posture which has entirely changed the mechanical principles involved in the function of the musculofascial structures which support the uterus and the uterine adnexa.

From the location and anatomic construction of the broad ligaments it seems reasonable to assume that nature has intended that they have an important function in maintaining the normal anterior position of the uterus. It is interesting to note that with none of the more popular operations for the cure of retroversion is reconstruction of the relaxed

quent pregnancies, he was convinced that the operation that had been devised was a marked improvement over procedures which utilized only the round ligaments to cure retrodisplacements of the uterus.

In 1927, Hurd⁵ reported on the end results of 1,000 retroversion operations that had been done by various methods at the Woman's Hospital and found that the Bissell operation had an incidence of recurrence of 1.8 per cent, the lowest for any operation which had been done during the period of time covered by his study.

The Bissell technique for the cure of retroversion has never received the attention which it deserves. The underlying surgical principle of the operation seems to be correct and in keeping with our modern conception of the function of the anatomic structures which support the

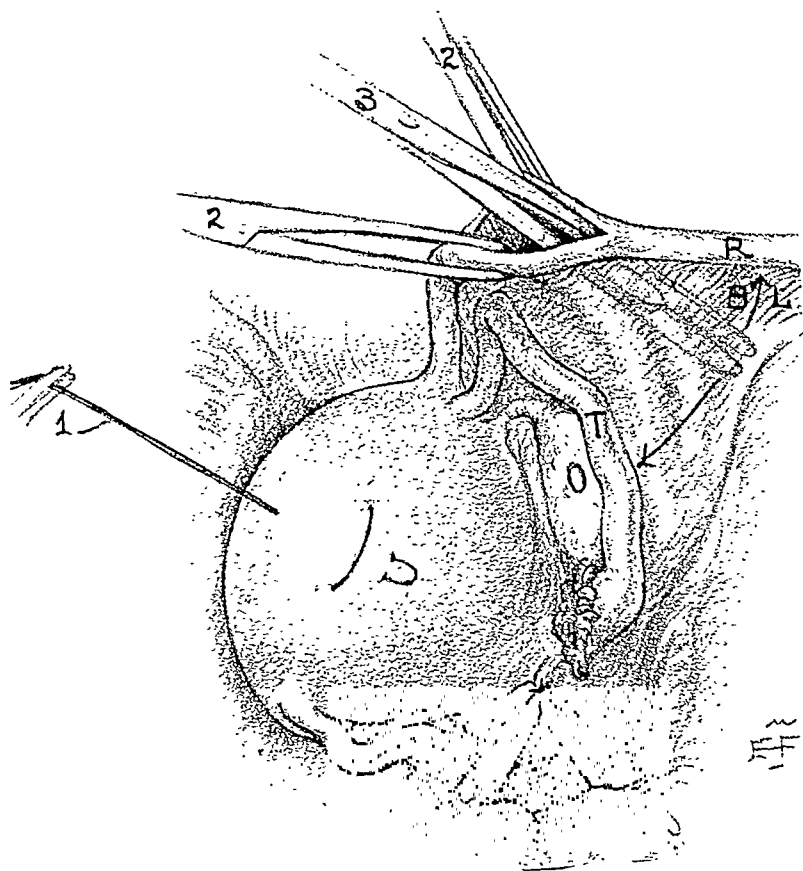


Fig. 4.—Shows the uterus (*U*) being drawn to the left by traction suture (1). The distal end of the round ligament (*R*), and broad ligament (*B.L.*) are being held under tension by two Allis clamps (2) placed on the margins of the incision made through the round ligament (*R*) as shown in Fig. 2. The avascular space between the two layers of endopelvic fascia (*E*¹ and *E*²), as shown in Fig. 3 is being opened by blunt dissection by means of a Sims artery clamp (3). The space is widely opened upward to the round ligament, outward to the lateral wall of the pelvis, and downward to the region of the cardinal ligament.

uterus in a normal anterior position. Certain members of the Woman's Hospital staff have used the operation with so much satisfaction for over twenty years that it seems worth while again to call the attention of gynecologists to this valuable technique and to emphasize the advantages which it appears to have over the round ligament operations that are usually employed for the cure of retroversion.

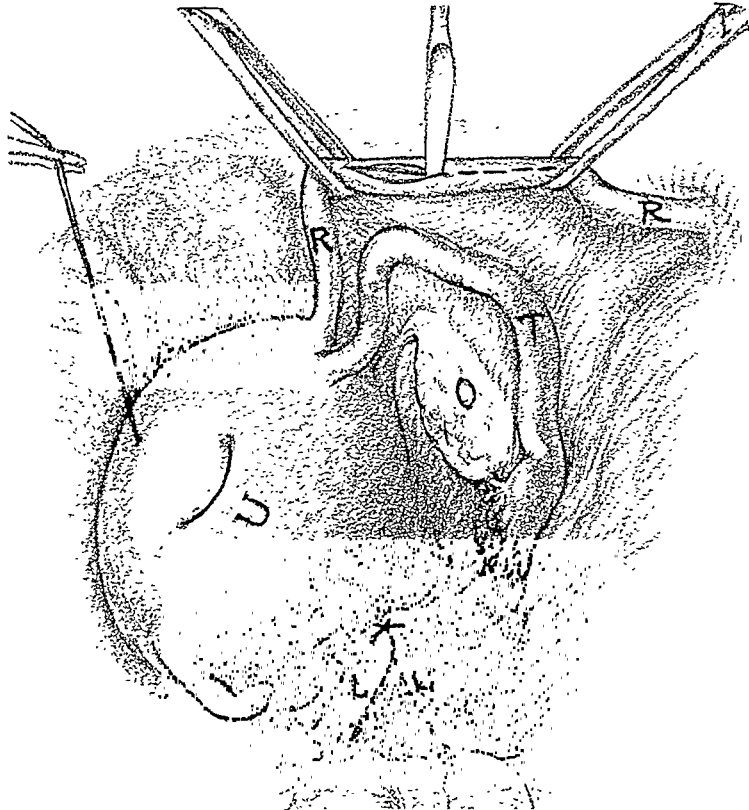


Fig. 2.—Shows the linen suture in the uterosacral ligaments (L), tied and the ligaments shortened. The uterus (U) is being drawn to the left side. The middle third of the round ligament (R) is being held under tension with two Allis clamps (I) so that it can be split longitudinally exactly in the midline throughout its entire thickness. This procedure is used as a means of approach to the avascular space between the two layers of endopelvic fascia contained within the structure of the ligament.

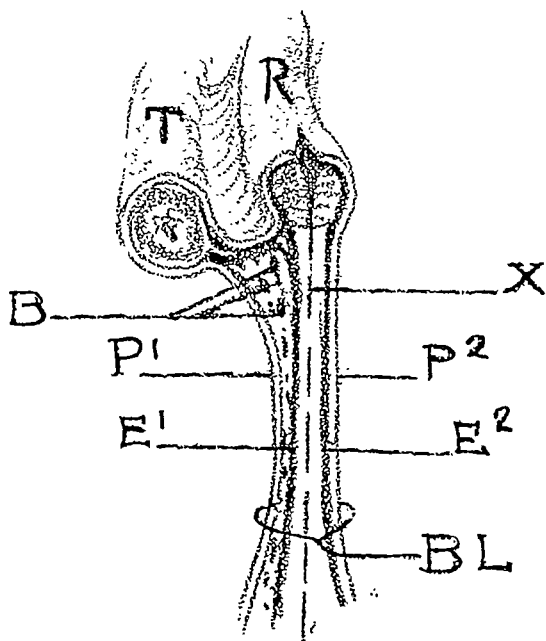


Fig. 3.—Shows a diagrammatic cross section of the tube (T), round ligament (R), and the broad ligaments (B.L.). The broad ligament (B.L.) is composed of four distinct layers of tissue, namely, two layers of peritoneum (P^1 and P^2) and two layers of endopelvic fascia (E^1 and E^2). The main blood vessels of the broad ligaments (B) are between the upper layer of peritoneum (P^1) and the upper layer of endopelvic fascia (E^1). A longitudinal incision through the center of the round ligaments (R) leads directly into an avascular space between the two layers of endopelvic fascia (E^1 and E^2) as represented by the dotted line X.

2. The method of shortening the relaxed upper layers of the broad ligaments tends to shift the structures which support the uterine adnexa toward the lateral walls of the pelvis, thereby effectively restoring normal position of the tubes and ovaries which are usually prolapsed when the uterus is retroverted.

3. Painful areas about the points of fixation of the round ligaments to the anterior abdominal wall are avoided.

4. Conditions for subsequent pregnancies are the same as though an operation for retroversion had never been done. In other words normal anatomic relationship of the pelvic organs and their supporting structures is restored without any change in the mechanical principles involved.

The disadvantage of the operation is that the technique is more time consuming and requires more surgical skill than the usual round ligament operations. Because the procedure requires more time, it may

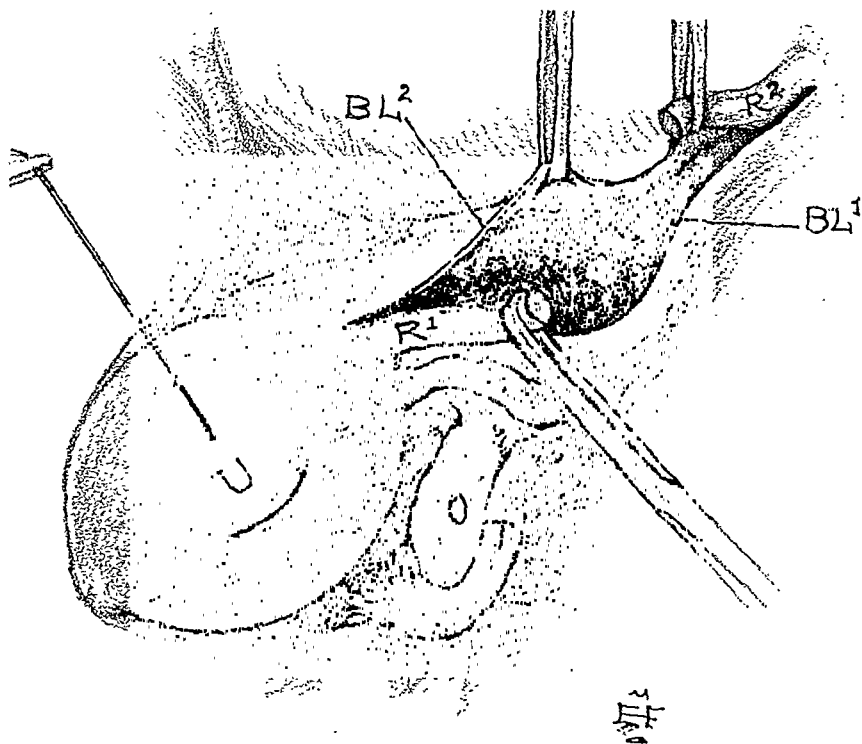


Fig. 7.—Shows the completed dissection. The upper and lower layers of the broad ligament (BL^1 and BL^2) are being retracted to demonstrate the avascular space between the two layers of endopelvic fascia in the broad ligament. The middle third of the round ligament has been excised. The upper layer of the broad ligament (BL^1) has been detached from the upper border of the distal one-third of the round ligament (R^2) and the lower layer of the broad ligament (BL^2) has been detached from the proximal one-third of the round ligament (R^1).

be unwise to combine it with an extensive vaginal plastic operation to repair birth injuries. It is our practice to adopt some simpler type of procedure when retroversion is complicated with adnexal inflammatory disease to avoid possible increased surgical risk as a result of extensive dissection of the broad ligaments.

Data regarding 376 operations for retroversion by the Bissell technique, performed from 1918 to 1939 inclusive, are recorded in Tables I to VII. The operations were performed by 21 members of the surgical staff.

The various steps in the technique as devised by Bissell are shown in Figs. 1 to 11.

COMMENT

From a study of the Bissell technique as described above, it is obvious that it requires painstaking dissection and careful reconstruction of the relaxed ligaments. However, the planes of cleavage are practically bloodless and the dissection can be easily and quickly carried out by any experienced surgeon.

The advantages of the operation are that:

1. Normal physiologic function of the relaxed round and broad ligaments is restored so that the uterus is supported as nature apparently intended it to be.

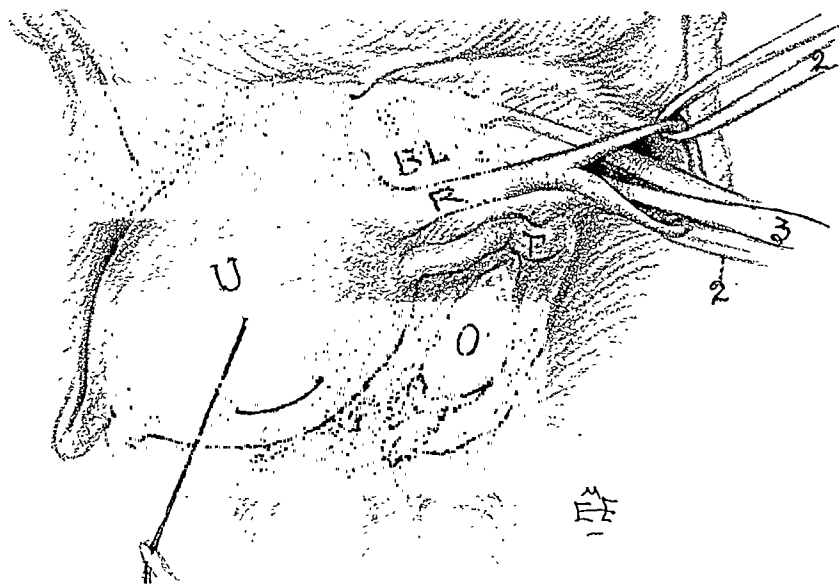


Fig. 5.—Shows the mesial ends of the round ligament (*R*) and broad ligament (*B.L.*) being held under tension by two Allis clamps (2) to allow completion of the opening of space between the two layers of endopelvic fascia (*E*¹ and *E*²), as shown in Fig. 2, by means of the Sims artery clamp (3). At the uterine end of the broad ligament (*B.L.*), the space is opened from the round ligament to the cardinal ligament area at the level of the internal os of the cervix and well up to the lateral margin of the uterus.

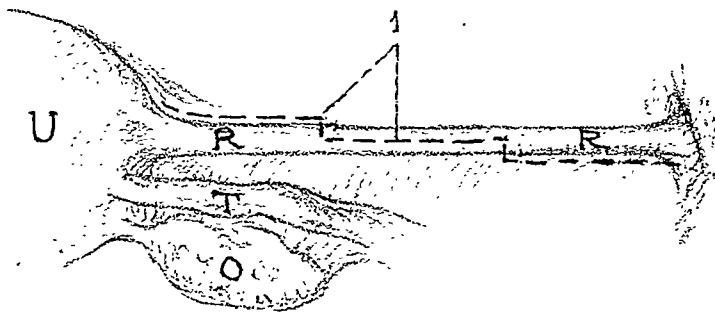


Fig. 6.—After the avascular space between the two layers of endopelvic fascia of the broad ligament has been freely opened as shown in Figs. 4 and 5, the lower layer (peritoneum and endopelvic fascia) is detached from the proximal end of the round ligament (*R*), and the upper layer (peritoneum and fascia) is detached from the distal end of the round ligament (*R*). The dotted line (1) shows the line of the longitudinal incision through the center of the middle third of the round ligament (*R*) and indicates the course of incisions used to detach the combined peritoneal and endopelvic fascial layers from the proximal and distal ends of the ligament. The middle third of the round ligament which was split longitudinally at the beginning of the dissection is then excised.

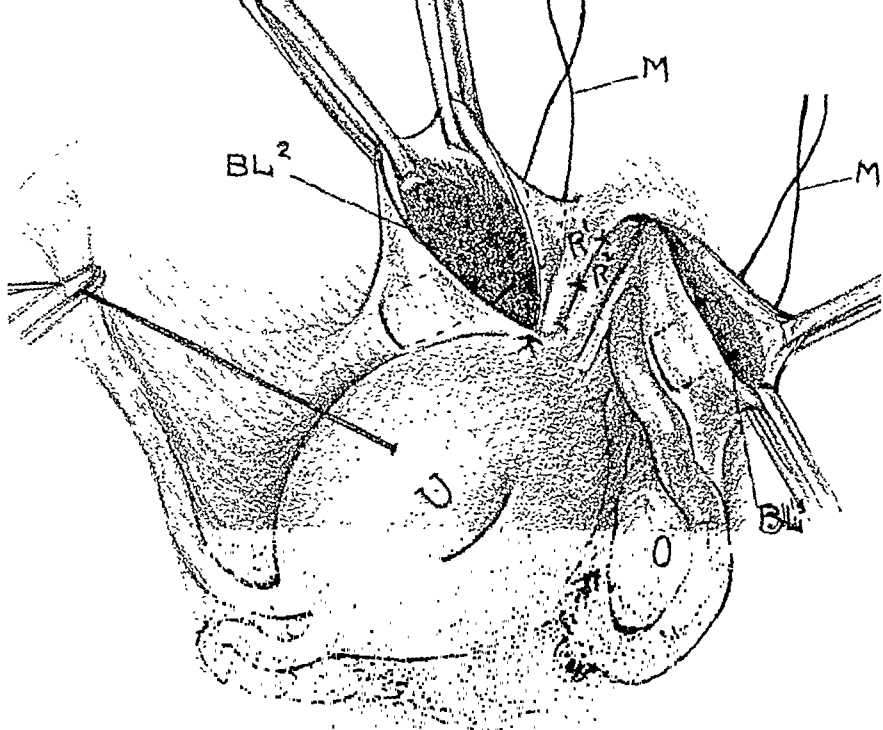


Fig. 10.—Shows the two portions of the round ligaments (R^1 and R^2) united to each other with interrupted sutures of chromic catgut No. 1. After the round ligament (R^1 and R^2) has been reconstructed it will be noted that both layers of the broad ligament are much relaxed, leaving a fold of the lower layer of the broad ligament (BL^2) near the uterus and a fold of the upper layer (BL^1) near the lateral wall of the pelvis. The relaxation in both these folds is taken up with mattress sutures (S) of chromic catgut No. 1.

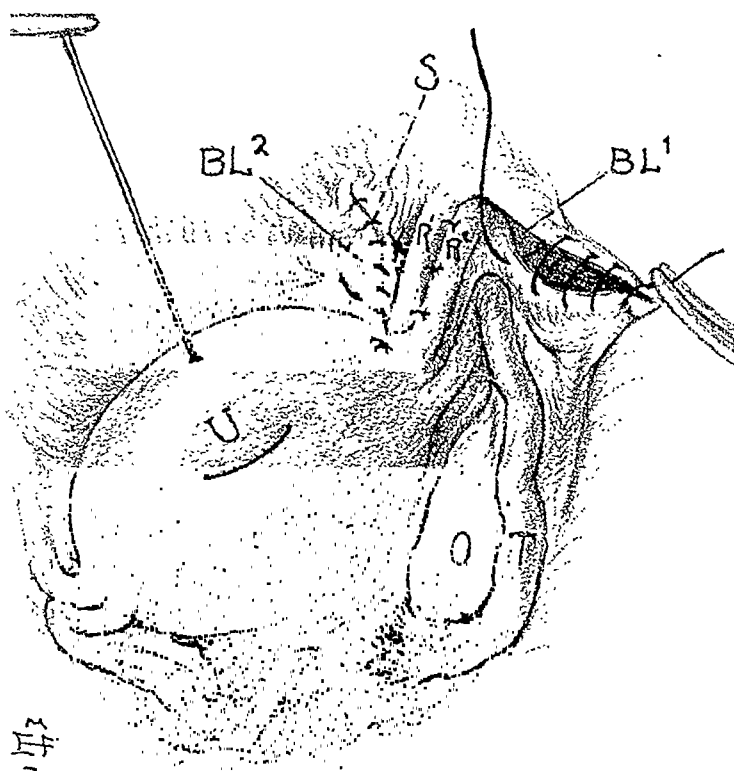
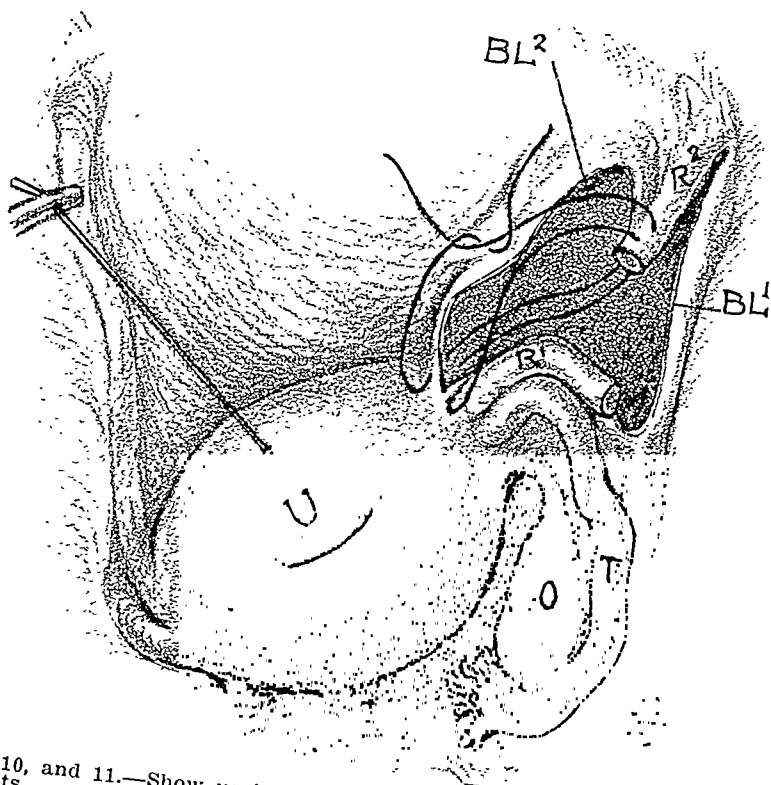


Fig. 11.—Shows the upper margins of each of these folds composed of peritoneum and one layer of endopelvic fascia whipped over with running sutures (S) of chromic catgut No. 1, thereby completing the reconstruction of the ligaments.



Figs. 8, 9, 10, and 11.—Show various steps in the reconstruction of the round and broad ligaments.

Fig. 8.—Shows the proximal end of the distal fragment of the round ligament (R^2) being sutured with linen into the denuded angle at the junction between the uterus (U) and proximal fragment of the round ligament (R^1).

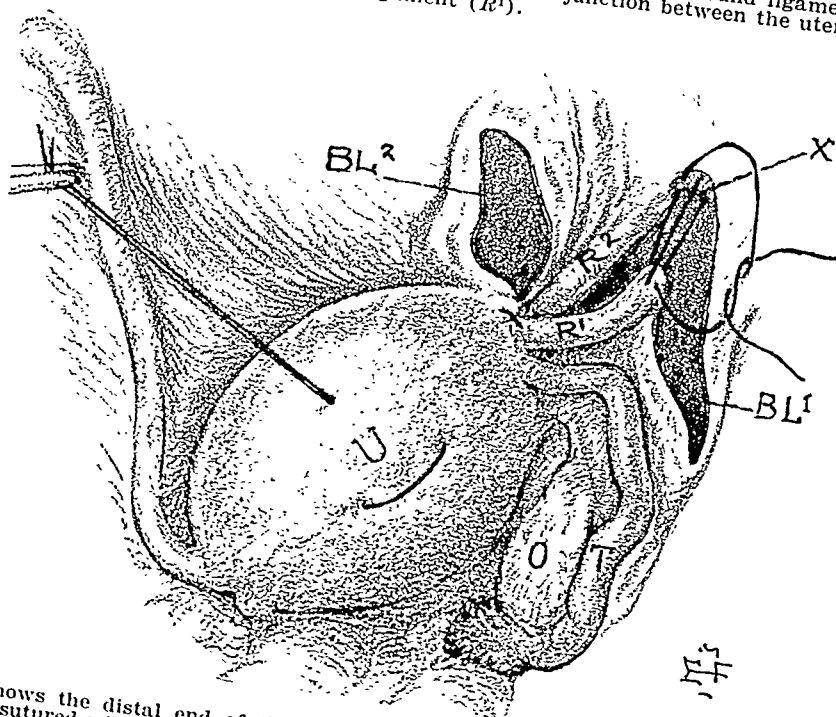


Fig. 9.—Shows the distal end of the proximal fragment of the round ligament (R^1) being sutured with linen to the fascial margin of the internal inguinal ring X .

TABLE IV. SUMMARY OF OPERATIVE PROCEDURES IN 376 CASES

Abdominal Operations:	
Operation for retroversion, Bissell technique	353
Operation for retroversion, modified Bissell technique	23
Operation for uterine adnexal disease	95
Separation of peritoneal adhesions	71
Shortening uterosacral ligaments	8
Appendectomy	289
Myomectomy	24
Vaginal Operations:	
Uterine curettage	134
Cauterization of cervix	38
Plastic operations on cervix	42
Plastic operations on vagina and cervix	14
Plastic operations on vagina	20
Hernia (inguinal 1, ventral 1, femoral 2)	4
Hemorrhoids	1

by the fact that 44.4 per cent of the 376 operations were performed by members of the staff upon their private patients. Table V is a summary of the varying periods of time during which 255 patients in the series were followed.

Table VI is a summary of the known facts regarding the pregnancies which occurred following operation in the 255 patients who were followed.

TABLE V. DURATION OF FOLLOW-UP OF 376 PATIENTS

MONTHS	NO. OF PATIENTS
1 to 6	34
6 to 12	49
12 to 18	41
18 to 24	54
Over 24	47
Over 36	52
Never examined	99
Total	376

TABLE VI. SUMMARY OF PREGNANCIES IN 255 PATIENTS FOLLOWED AFTER OPERATION

64 women had 73 pregnancies with the following outcome:	
Spontaneous abortion	19
Induced abortion	2
Therapeutic abortion (Cardiovascular disease)	1
Delivered at term	39
Pregnant when last examined	12
Total	73

TABLE VII. SUMMARY OF FAILURES FOLLOWING OPERATION FOR RETROVERSION IN 376 CASES

OPERATION	NO. OF OPERATIONS	NO. FOLLOWED AFTER OPERATION	NO. OF FAILURES	INCIDENCE OF FAILURE PER CENT
Bissell Standard technique	353	255	5	1.9
Bissell Modified technique	23	22	1	4.5
Total	376	277	6	2.1

When unsatisfactory results occur following the Bissell operation, it is the conviction of surgeons who have used the technique that they are

Table I shows the high incidence of patients that were operated upon within the childbearing period.

TABLE I. DISTRIBUTION OF 376 CASES AS REGARDS, COLOR, MARITAL STATUS AND AGE

<i>Hospital Status:</i>		AGE INCIDENCE	
		YEARS	NUMBER
Private patients	167	Up to 20	16
Ward patients	209	20 to 25	91
<i>Color:</i>		25 to 30	129
White	336	30 to 35	84
Colored	40	35 to 40	38
<i>Marital Status:</i>		40 to 45	10
Single	61	No record	8
Married	315	Total	376

TABLE II. RECORD OF PREGNANCIES IN THE 376 PATIENTS PREVIOUS TO OPERATION

115 patients had never been pregnant.
95 patients had had 151 <i>spontaneous abortions</i> .
23 patients had had 45 <i>induced abortions</i> .
219 patients had had 426 <i>term pregnancies</i> .
Total No. of pregnancies 622.

Although 376 of the patients had had 622 pregnancies, many either complained of sterility or wished subsequent pregnancies.

TABLE III. SUMMARY OF CHIEF PREOPERATIVE COMPLAINTS IN THE 376 CASES

	TOTAL
1. Pain:	234
Lower abdomen and pelvis	135
Backache	97
Rectal	2
	<hr/> 234
2. Menstrual Disorders:	72
Dysmenorrhea	31
Menorrhagia	20
Metrorrhagia	15
Irregular menses	5
Amenorrhea	1
	<hr/> 72
3. Sterility	16
4. Leucorrhea	15
5. Vaginal protrusion (birth injuries)	12
6. Miscellaneous	20
7. No record	7
	<hr/> 376

In taking histories, it is the routine custom at the Woman's Hospital to record physical complaints in the order of their importance in the minds of the patients. Table III is a summary of the chief complaints as recorded on the 376 case histories reviewed for this study.

Table IV shows the type and number of abdominal and vaginal operations that were done in addition to the 376 operations for retroversions. The uterosacral ligaments were shortened in only 8 cases. Although the principle involved in this step in technique appears to be correct, it is obvious that good results can be achieved without it.

Follow-up records were available in only 255, or 67.8 per cent, of the 376 patients operated upon. Difficulties in getting satisfactory follow-up records were increased

2. Unless it is known that retroversion preceded pregnancy, post-abortual and post-partum retroversion should be treated by palliative means to reduce the incidence of permanent retrodisplacements of the uterus.

3. Selection of cases for treatment by surgical means should be based on painstaking physical examinations and therapeutic tests to be sure that preoperative pelvic symptoms are gynecologic in origin.

4. Associated functional and pathologic conditions of the uterine adnexa more frequently constitute indications for operation than retrodisplacement of the uterus.

5. Operations for the cure of retroversion and its associated conditions should usually be aimed at preserving the child-bearing function and establishing anatomic and physiologic conditions which will be favorable for subsequent pregnancies.

6. Retroversion of the uterus is caused by relaxation of the broad as well as the round ligaments.

7. Operations for the cure of retrodisplacements of the uterus should be done by techniques which restore the function of the broad as well as the round ligaments.

8. The incidence of failure in operations for retroversion could probably be reduced if conception could be postponed until at least six months after operation.

REFERENCES

- (1) *Rubin, I. C.*: Obstetrics and Gynecology, 3: Philadelphia and London, 1933, W. B. Saunders Co., p. 173. (2) *Findley, W. M.*: AM. J. OBST. & GYNEC. 24: 874, 1933. (3) *Crossen and Crossen*: Operative Gynecology, St. Louis, 1938, The C. V. Mosby Co., p. 353. (4) *Bissell, Dougall*: AM. J. Obst. 74: 1, 1916. (5) *Hurd, R. A.*: AM. J. OBST. & GYNEC. 13: 742, 1927.

33 EAST 68 STREET

DISCUSSION

DR. JOSEPH L. BAER.—This eloquent plea for the survival and wider recognition of the Bissell operation for retrodisplacement is worthy of the best traditions of a great hospital. The speaker showed magnificent results for this operation.

I am in complete accord with much that the essayist has said. However, I am in complete and fundamental disagreement with him on the role of the round ligaments. I believe they play no part in the establishment and maintenance of antedisplacement of the uterus. Therefore, I believe they have nothing to do with the development of retrodisplacement. They have one obvious function. They are massive guy ropes which help to fix the fundus uteri when the uterus goes into labor. Palpation of the abdomens of women in labor frequently reveals on one and sometimes both sides a remarkable hypertrophy of the round ligaments. If the patient has an obstruction, the obvious role of these round ligaments must be clear. They are fixation points for the fundus uteri when the organ is in labor. Inspect the pelvis in a nullipara in whom there is normal antelexion. As one looks in from the open abdomen the round ligaments can be seen describing an enormous arc from the cornua to the internal inguinal ring, underlying the anterior peritoneum of the broad ligaments, completely relaxed and much longer than the distance between the cornu and the ring on the same side. Displace that fundus backward into the cul-de-sac as far as you please and you will see that the round ligaments do not become taut. How can such structures be given credit for the maintenance of normal anteplacement of the uterus? The erect posture and the consequent rotation of the pelvic girdle as the infant child begins to walk, the growth and descent of the uterus into the true pelvis with adolescence, these, I believe, are the steps which result in pressure

due to undercorrection of the attenuated ligaments at time of operation rather than to their subsequent relaxation.

The following is a summary of the records of the 6 cases in which operations for retroversion by the Bissell or modified Bissell techniques failed.

1. Mrs. McD. (22490), aged 28 years, white, nulliparous. Chief complaint: irregular excessive periods. Operation: Uterine curettage, Bissell operation for retroversion, separation of peritoneal adhesions, appendectomy, and femoral hernioplasty. Observed for four months after operation. Uterus retroverted second degree at last visit.

2. Mrs. B. (40393), aged 26 years, white, had had one induced abortion and one term pregnancy. Chief complaint: Pelvic pain. Operation: Retroversion (modified Bissell). History of acute pelvic inflammatory disease within six months after operation. Term pregnancy starting sixteen months after operation. Observed for eighteen months. Uterus completely retroverted after pregnancy.

3. Mrs. W. (34020), aged 25 years, colored, had had one term pregnancy. Chief complaints: Irregular menses and pelvic pain. Operation: Uterine curettage, retroversion (Bissell), appendectomy. Difficult term delivery in another hospital one year after operation. Observed thirty-seven months. Uterus retroverted second degree.

4. Mrs. H. (34324), aged 21 years, white, had had one spontaneous abortion. Syphilis at nineteen years. Chief complaints: Pelvic pain and dyspareunia. Operation: Retroversion (Bissell), appendectomy, separation of adhesions. Delivery one year after operation by difficult medium forceps; baby was eleven days postmature. Weight of baby 8 pounds 12 ounces. Observed for eighteen months after operation. Uterus was completely retroverted.

5. Mrs. P. (34722), aged 27 years, white, nulliparous. Chief complaint: Metrorrhagia. Operations: Retroversion (Bissell), separation of adhesions. Treated in clinic for acute pelvic inflammatory disease within six months after operation. Observed for thirty-seven months. Uterus completely retroverted.

6. Mrs. C. (32262), aged 28 years, white, had had 2 spontaneous abortions and 2 term pregnancies. Had been treated for syphilis. Previous appendectomy. Chief complaints: Backache and pelvic pain. Operations: Trachelorrhaphy, repair of laceration pelvic floor, retroversion (Bissell), separation of adhesions. Discharged from follow-up in 1925, twenty-eight months after operation. Uterus completely retroverted. Readmitted fifteen years later for operation for chronic adnexal disease and fibroids.

In the above case histories it will be noted that follow-up records showed that of the 6 failures, 5 were after the standard Bissell technique and one after a modified Bissell technique. Factors contributing to the failures may have been acute pelvic inflammatory disease within six months after operation in 2 cases; a modified Bissell technique in 1 case; pregnancy and delivery within one year in 1 case, and pregnancy and difficult medium forceps delivery of an 8 pound 12 ounce postmature baby in 1 case.

The Bissell technique requires more surgical skill than the usual round ligament types of operations. Four of the 6 failures occurred in patients operated upon by resident surgeons under supervision.

SUMMARY

To summarize some of the facts regarding retroversion, and the relationship of retroversion and its associated conditions to pregnancy, it may be stated that:

1. These conditions are not infrequently the cause of sterility, early abortion, and unpleasant symptoms following abortion and delivery.

symptoms are not due to the retroversion ordinarily but to the accompanying pathology. The backaches associated with retroversion usually clear up when the accompanying erosion or endocervicitis has been cured. The dysmenorrhea of retroversion also clears up when the cervical pathology, be it an erosion, endocervicitis, or stricture of the cervix, has been done away with, as well as the menorrhagia. At the Presbyterian Hospital last year only seventeen patients were operated upon "for retroversion." Upon a stricter analysis, however, I am quite certain that in most cases the retroversion was not the reason for the operation but was a condition which accompanied the pathology necessitating the operation, such as endometriosis, ovarian cyst, infected appendages, etc. As my experience in gynecology increases the importance of retroversion as a clinical important condition decreases.

DR. ALDRIDGE (closing).—In the discussion Dr. Baer has stated his conviction that the round ligaments have nothing to do with supporting the uterus in an anterior position. He has also reviewed certain theories as to conditions which may cause retroversion. They should be regarded as no more than theories because the exact cause of retroversion has not been established.

In presenting the results of our experience with the Bissell operation, the statement was made that the uterus is held in an anterior position by the normal function of the round and broad ligaments. Regardless of whether this statement is accepted, we are convinced that combined reconstruction of the round and broad ligaments by the Bissell technique, gives us a higher incidence of satisfactory end results in the surgical cure of retroversion than with any other procedure which we use. Furthermore, in a limited series of cases, we have been impressed with the success of the operation in withstanding the strain of subsequent pregnancies.

Dr. Baer favors parametrial fixation, a procedure developed for the cure of prolapse, as the operation of choice to cure acquired retroversion. Although uterine retroversion and uterine prolapse often occur together in the same patient, from the etiologic standpoint we regard the two conditions as distinct clinical entities. We consider the principle involved in parametrial fixation anatomically correct for the cure of prolapse but not for the cure of retroversion. We have no more confidence in parametrial fixation for the cure of retroversion than we have in retroversion operations for the cure of uterine prolapse.

Dr. Heaney has emphasized the importance of associated pathologic pelvic conditions in the causation of symptoms often attributed to the retroversion itself. He believes that if cervical erosion and infection are eradicated, a retroverted uterus will usually assume a normal anterior position. There is evidence to suggest that cervical infections may result in some loss of tone of the structures that support the uterus. However, in our experience, spontaneous cure of retroversion, following successful treatment of cervical infections, is so rare that it cannot be looked upon as a reliable method of treatment for chronic retrodisplacement of the uterus.

Essenberg, Schwind, and Patras: The Effects of Nicotine and Cigarette Smoke on Pregnant Albino Rats and Their Offspring, *J. Lab. & Clin. Med.* 25: 708, 1940.

Among others the following results were obtained in a study of a large number of nicotine-injected and smoked female rats and their offsprings: Two-thirds of all the young of treated mothers were underweight and remained so for some time. Of the females injected with nicotine, 63 per cent lost one or more, and 33.3 per cent all of their young. In those exposed to tobacco smoke, these percentage figures were 28 and 13.5, respectively. In both groups, temporary sterility, resorption of young in utero, and abortions were noted.

The writers' final conclusion is: A marked parallelism exists between treated rat females and their young, and human mothers and their young in cases where the mother is a heavy smoker or is employed in the tobacco industry.

HUGO EHRENFEST.

against the posterior surface of the uterus, thus turning, bending and holding it forward against the bladder and symphysis. The 20 per cent of normal nulliparas who have retrodisplacement without symptoms have it either as a result of failure of this rotation mechanism or defective development of the genitalia themselves.

So long as normal development takes place in the infant girl who has normal genitalia, there is also normal antedisplacement of the uterus, not by virtue of the round ligaments but by virtue of the play of intra-abdominal forces. The corpus uteri, freely movable, riding on a flexible joint, is forced forward; it stays there as long as the parametrium and paracolpium remain adequate and the space between the bladder and the uterus remains free of bowel.

How then do we explain the splendid results shown in this paper? The essayist has pointed out that the feature which distinguishes the Bissell operation from other round ligament shortening methods and gives it added merit, is the puckering of the underlying broad ligament structures. Here we are dealing with peritoneal folds overlying the thinnest possible areolar tissue. I cannot believe that that is the answer for the success which has been attained with the Bissell procedure. This operation succeeds because it utilizes available structures to pull the fundus forward. This keeps the bowel out of the vesico-uterine angle and exposes the dorsum of the uterus to the sustaining effect of intra-abdominal pressure. Its grave disadvantage compared with the other round ligament shortening operations is the time it must consume.

I am convinced that the four types of retrodisplacement which were described, namely, those developmental in origin, those following the trauma of childbirth, those following adnexal and other inflammatory diseases of the pelvic cellular tissue, and the acute traumatic type, should each be treated differently if they require treatment at all. Certainly we today do very many less operations for retrodisplacement than we did twenty years ago. We are much more conservative, and we do a much better job of attempting to treat the real pathology. Only if we can convince ourselves that the retrodisplacement causes symptoms do we proceed to surgery for its correction.

Retrodisplacement following the trauma of childbirth is primarily due to injuries of the superior fascial plane which is the true support of the uterus. As was accurately pointed out by Dr. Aldridge, we have the cardinal ligaments laterally, the pubovesical fascia anteriorly, and the uterosacral ligaments posteriorly. Injury to some of these fascial structures results in a sagging of the uterus. The intestinal coils enter the vesicouterine space anteriorly and the intra-abdominal force does the rest. Surgical cure here is complete reconstruction of the fascial planes, that is by parametrial fixation plus whatever else need be done in the reconstruction of the birth canal.

Retrodisplacement caused by adnexal disease requires abdominal approach, a round ligament shortening with bladder advancement. Uterosacral plication is logical and reliable. The Gilliam suspension operation is entirely dependable if one knows how to carry it out. It will allow for childbirth if the attachment is kept sufficiently away from the symphysis, and the risks of intestinal obstruction are avoided if the attachment is snug.

The women who have normal retrodisplacement without symptoms require no treatment. The acute traumatic type of retrodisplacement requires only immediate replacement and adequate rest to establish a complete recovery.

In the decade from 1920 to 1930, there were 337 operations for retrodisplacements done by the Gynecological Staff of Michael Reese Hospital. Of these, 239 were primary and 98 were secondary to other pathology. In the decade from 1930 to 1940, there were 358 operations for retrodisplacements, of which 230 were primary and but 28 secondary. In the first decade, from 1920 to 1930, the Gilliam suspension operation was the operation of choice, while in the second decade parametrial fixation was done largely. In both decades many other procedures were used. In the total of 695 operations, there were 5 known failures, 2 Baldy-Webster, 2 ventral fixation, and 1 Barrett operation. This is only a slightly higher percentage than the essayist reported for the Bissell operation.

DR. N. S. HEANEY.—I would like to discuss the role of retroversion of the uterus in the production of the symptoms usually attributed to it. In my opinion the

force proportionate to the degree of distention. If nothing is distending it, the sphincter does not contract, but once it has been opened by trigonal action and stretched by fluid passing through it, the muscle tends to close. Whether this reaction is affected by nervous plexus or is a purely muscular phenomenon remains to be determined, but the loss of this "reactive contraction" mechanism undoubtedly contributes much to disability of the female bladder.

With a cough, sneeze, or other strain which produces a rise in intra-abdominal pressure, the voluntary sphincters are brought into play, and normally these are sufficient to provide the added barrier necessary to resist the associated rise in intracystic pressure.¹² With loss of internal sphincter tone, it is probable that the external voluntary sphincter is sufficient to preserve continence while the patient is quiet.¹³ But the normal state of balance is disturbed, and the patient has no additional barrier to employ against the sudden (but not necessarily large) rise of bladder pressure associated with laughing, coughing, or sneezing.

Since urinary incontinence, regardless of exact etiology, represents a momentary increase in the forces of urinary expulsion over the powers of urethral resistance, it would appear that incontinence could result from (a) an increase in urinary expulsive force or intravesical pressure, (b) a lowering of the powers of resistance or urethral sphincter action, or (c) a combination of (a) and (b).

(a) *Increase in Urinary Expulsive Force.*—The partial incontinence which so often develops in the last trimester of pregnancy, and that associated with large pressure-producing pelvic tumors are clear examples of incontinence chiefly on the basis of elevated intravesical pressure. But aside from these, the actual causative relationship between increases of intravesical pressure and diurnal incontinence is difficult to prove.

In an effort to evaluate the rôle played by the forces of expulsion in stress incontinence, we have performed over 80 cystometric studies on 32 patients with some degree of pelvic floor relaxation.¹⁴ Fig. 1 is an illustration of three such curves obtained on the same patient. Curve B is a postoperative study, and represents a normal cystometric reading. Curve C is a preoperative study obtained in the traditional manner, and reveals a bladder of somewhat increased capacity with pressures slightly lower than normal. But the cystometrogram A is also a preoperative study on the same patient, and by comparison with C, this shows a relatively small capacity bladder of higher intravesical pressure. The essential difference in the obtaining of these two readings was that in curve A, the patient's descensus was drawn down to the position it occupied while she was on her feet. In other words, the descensus uteri in this case could produce a relative increase of intravesical pressure while the patient was standing which would not have been indicated by the traditional cystometric reading performed with the patient recumbent.¹⁵ In like manner it can be shown that pressure producing tumors (Fig. 2), and large rectoceles which press against the bladder result in relative rises in intravesical pressure.

We are not suggesting that these conditions are frequent causes of stress urinary incontinence in women. Nevertheless, since the ultimate objective of treatment is to restore a balance in which the powers of urethral resistance are greater than the forces of urinary expulsion, it is well to bear in mind that

A METHOD FOR EVALUATING THE STRESS OF URINARY INCONTINENCE

ALLAN C. BARNES, M.D., ANN ARBOR, MICH.

*(From the Department of Obstetrics and Gynecology, University of
Michigan Hospital)*

THE importance of the problem of stress urinary incontinence in women is well recognized. The complaint is highly embarrassing or even incapacitating to the patient; it is met with frequently and its cure is difficult. The sizable literature which has appeared on this topic attests to the fact that this problem is far from settled. Many contributions have added new operations or new operative modifications to the already crowded list of therapeutic measures. However, a survey of some of the reported results of these operative procedures indicates that the percentage of patients cured ranges from 36 to 100 per cent, with an average for any particular procedure close to 80 per cent.^{1-9, 13, 23} In general, the number of cures diminishes in direct ratio to the length of time allowed to elapse between operation and the follow-up studies. And the fact that from 6 to 14 per cent of the reported cures have been in patients subjected to repeated operations serves as a further indication that the therapeutic situation in respect to this complaint is not entirely satisfactory.

It has been the opinion in this clinic that a sufficient number of well-established operative procedures are already available for the treatment of incontinent patients. It has been frequently demonstrated that certain of these can give satisfactory results when judiciously chosen and applied with a knowledge of the underlying disturbance of function. Therefore no new surgical procedures are described in this paper. It presents rather a clinical and investigative review of the fundamental factors in the pathologic physiology of stress urinary incontinence, together with a clinical test to serve as an aid in its correct evaluation and the selection of the proper operation.

PHYSIOLOGIC CONSIDERATIONS

In the normal female at rest, the involuntary urethral sphincter will retain urine in the bladder. This principle has been so clearly demonstrated by the excellent work of Denny-Brown and Robertson,¹⁰ that extensive discussion here is not necessary. It is well to bear in mind, however, the nature of involuntary sphincter action. With the bladder at rest the internal sphincter is firmly closed, but it is not in a state of continuous contraction. Involuntary sphincters do not maintain "unmeaning contraction."¹¹ If from its resting closed state an involuntary sphincter is gradually distended, it will exert a contractive

EVALUATION OF FUNCTIONAL DISABILITY

The accurate diagnostic evaluation of patients with partial urinary incontinence has not in the past been easy. The patient's history and the physical examination do not tell the entire story, for seemingly mild cases will unpredictably resist every form of therapy attempted. More information than the degree of pelvic relaxation, if any, and the patient's description of her symptoms is necessary for the competent selection of the proper operative procedure.

During the past year we have been employing in this clinic a test based on the physiologic principles outlined above, and designed to give additional diagnostic information necessary for the thorough evaluation of these cases. It consists essentially of three studies, all relatively easy to perform.



Fig. 3.—Normal anteroposterior sphincterogram. Balloon shadow obliterated by urethral resistance, leaving balloon dilated only inside internal and outside external meatus.

1. *Measurement of Intravesical Pressure.*—With a standard volume of fluid in the bladder, and with the patient standing, direct manometric readings are obtained.²² We have optionally selected 3½ ounces of physiologic saline solution, and have determined normal readings on a group of continent patients. For the occasional patient who cannot accommodate 3½ ounces, the bladder is filled to capacity and the reading (usually found to be markedly elevated) is taken. Since most partial incontinence is suffered while the patients are active and on their feet, we feel that the standing position in which this reading is taken provides a more useful comparative figure.

intravesical pressures may frequently be elevated, thereby making increased demands on the urethral sphincter mechanism.

(b) *Decrease in Urethral Resistance.*—Damage to the sphincter mechanisms or their supporting structures may lower their efficiency to such an extent that they are unable to preserve continence. While this principle is a generally accepted one, the manner in which damage may occur, and the exact nature of such damage, has not been conclusively demonstrated. Most frequently the trauma of childbirth is assumed to be the chief cause of injury to the mechanism of urinary continence. While it is true that 150 patients with incontinence had a higher average parity than 140 continent parous women of the ward service at the University Hospital (4.8 children apiece compared to 3.6), we have also had two nulliparous patients with stress incontinence, and one of our most severe cases occurred in a para i who had a short easy labor, giving birth to a 5-pound child. The theories concerning the nature of the damage to the urethral sphincters are legion. A complete cataloguing of these theories would be of no value here. Suffice it to say that they all fall principally into two groups: those maintaining the primary damage to be on the

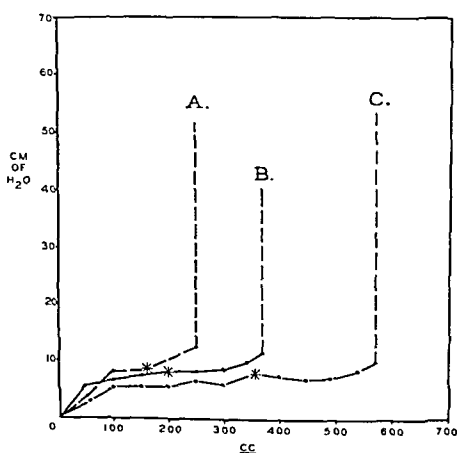


Fig. 1.

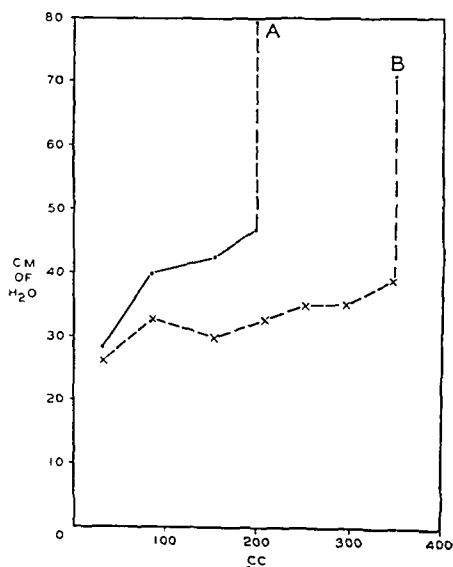


Fig. 2.

Fig. 1.—Three cystometric curves from the same patient (see text).

Fig. 2.—Preoperative (A) and postoperative (B) curves on patient with bilateral large ovarian fibroma. Cystometries obtained with patient sitting up.

urethra or its sphincters,^{16, 17} and those stating that the essential changes involve peri-urethral or supporting tissues.^{18, 19} In all probability the problem is not one of "either . . . or," but of "both . . . and."^{20, 21}

The degree of the functional damage may be interpreted from the clinical history obtained. At onset the incontinence often seems to result from a failure on the patient's part to augment her sphincter mechanism rapidly enough. If she sneezes several times in succession, she will be incontinent only with the first sneeze. The reflex muscular tightening which reinforces the sphincter mechanism in the face of increased intra-abdominal pressure is delayed rather than completely lost. Subsequently there may be incontinence associated with all coughing, laughing or other relatively rapid changes in intra-abdominal pressure, while continence is preserved on lifting heavy objects, or in other situations where ample time may be taken to adjust the musculature to the increased strain. Finally there is complete incontinence on all activity or even incontinence while the patient is recumbent.

the bladder.¹⁰ Hence, in this x-ray the bladder floor should be flat at the urethrovesical junction, and should have the relationship with the urethra of two straight lines to each other. Funneling of the bladder floor toward the urethra indicates that mere increase in intravesical pressure, unassociated with contraction of the trigone, has forced fluid through the internal sphincter, and denotes a weakening of this sphincter.²⁵ Examples of this situation are shown in Figs. 7 and 8.



Fig. 6.—Normal oblique view, with watch chain in urethra. Despite the fact that the patient is straining, internal sphincter area (A) shows no funneling.

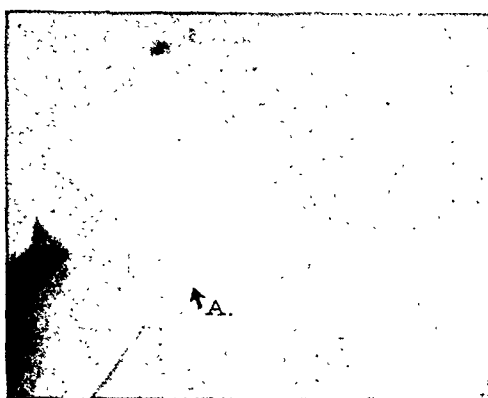


Fig. 7.

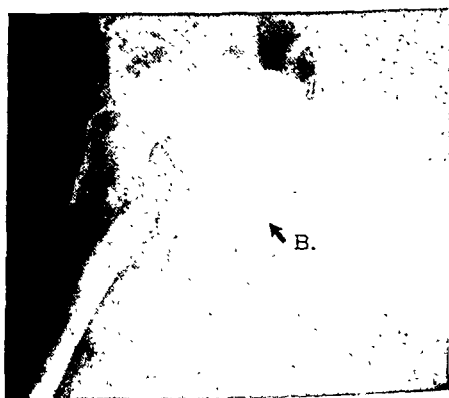


Fig. 8.

Figs. 7 and 8.—Two variations from the normal oblique view. Marked relaxation (A) and minimal funneling (B). See also Fig. 10.

The information obtained from these studies permits a much better understanding of the patient's incontinence. With such information in mind, a complete program for the treatment of partial incontinence in women should include measures designed to (a) lower intracystic pres-

2. *Direct Measurement of Urethral Resistance.*—The method we have adopted for measuring the strength of urethral resistance is a modification of an experiment performed some years ago by Kennedy.²³ A small balloon composed of two superimposed finger cots is inserted in the urethra, filled to a known manometric pressure with a 90 per cent sodium iodide solution, and an x-ray taken. Studies on normal patients indicate that under these conditions the entire urethra should remain closed and obliterate the balloon shadow at a pressure of 35 cm. of fluid, and it is at this pressure that the x-ray is taken. The result in a normal patient is shown in Fig. 3. The bladder is filled with 180 c.c. of an 8 per cent solution of sterile sodium iodide, which is well tolerated, and the balloon is seen to be compressed throughout the length of the effective resistant force of the urethra. The essential point to be observed in this film is whether or not the dilatation of the balloon at its inner end lies



Fig. 4.



Fig. 5.

Figs. 4 and 5.—Two abnormal anteroposterior sphinctometrics, showing varying degrees of weakness at internal sphincter area. Balloon dilates at inner end before urethrovesical junction is reached (A and B). Compare with Fig. 3.

within the bladder shadow. In other words, the effective urethral resistant force must reach the urethrovesical junction. Variations from this normal picture occurring in two patients with differing degrees of sphincteric weakening are shown in Figs. 4 and 5.

3. *Indirect Measurement of Internal Sphincter Strength.*—This determination is also made in conjunction with x-ray, the film being taken in the oblique, and an indwelling watch chain used to mark the course of the urethra as suggested by Stevens and Smith²⁴ (Fig. 6). As this film is exposed, the patient is asked to strain down as hard as she can. With straining intravesical pressures from 60 to 80 cm. of water may be obtained, so that in this study the urethra is subjected to a much greater force than in the first film, but it is a force applied in a more physiologic manner, i.e., from within outward.

In a normal person, a rise in intravesical pressure alone cannot force fluid through the internal sphincter without a detrussor contraction of

structure: d'Azevedo and Campos²⁶ (loss of angle of urethra to bladder floor), Taylor and Watt²⁷ (descent of posterior urethral wall), and Thomsen²⁸ (loss of anterior angulation of urethra). Our x-rays have not confirmed a constant association of these factors with incontinence, whereas continent patients have demonstrated wide variation in urethral angulation. To the patient, function rather than shape is important; a single band able to resist pressure is more valuable than a normally shaped urethra with no inherent power of effective resistance.

Fig. 12.

Fig. 13.

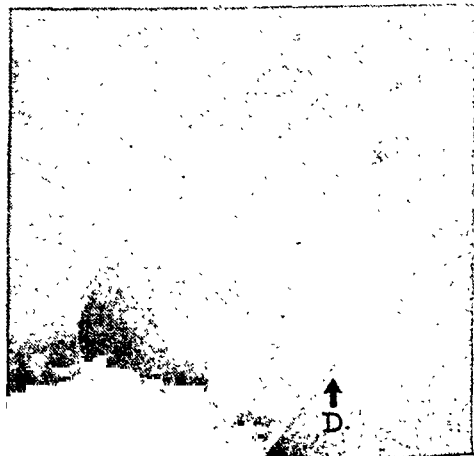


Fig. 14.

Fig. 15.

Figs. 12 to 15.—Urethral resistance fails, as shown at A, outside bladder. Postoperatively internal sphincter area (B) resists pressure satisfactorily. Funneling (C) at internal sphincter area corrected by plastic, restoring bladder floor and sphincteric resistance (D). Compare postoperative view (Fig. 15) with normal (Fig. 6).

The same type of x-ray studies used in the preoperative evaluation of the patient's disability give a postoperative indication of whether or not effective urethral resistance has been restored. Fig. 9 is the pre- and postoperative antero-posterior view of a patient who had a Kelly stitch type of operation. In the view on the left, the dilatation of the inner end of the balloon can be seen to begin just outside the bladder. Postoperatively, as shown in the film on the right, the urethral ability to contract extends, as it should normally, all the way to the urethrovesical junction. Figs. 10 and 11 are oblique studies before and after simple Kelly stitch. The funneling at the urethral vesical neck is minimal, but postoperatively it is obliterated, and the patient is continent.

In like manner, Figs. 12 to 15 give the preoperative (to the left) and postoperative studies of a patient who was a candidate for a plastic operation. The

sure where this is found to be increased, and (b) re-establish urethral resistance where this is diminished.

(a) In a patient with pelvic relaxation and descensus, plastic repair will lower the elevated intravesical pressure. Obtaining intravesical pressure readings pre- and postoperatively on 34 patients has shown that procedures which include plaiting of the pubovesicocervical muscle layer, correction of rectoceles, or operations for the removal of large uterine or ovarian tumors accomplish this result.

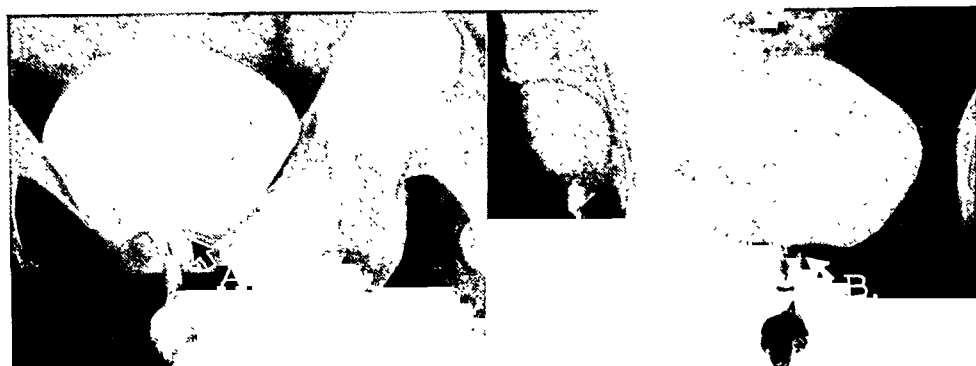


Fig. 9.—Preoperative (left) and postoperative (right) sphinctometric. Minimal relaxation indicated by dilatation of balloon at A outside bladder. Following Kelly stitch this is corrected (B).



Fig. 10.



Fig. 11.

Figs. 10 and 11.—Minimal funneling at A preoperatively. Bladder floor flat at B following Kelly stitch.

While causative relationship between increased forces of expulsion and stress incontinence cannot be completely demonstrated and is not here claimed, every gynecologist has encountered cases of incontinence cured by nothing other than plastic repair, and the associated reduction in intravesical pressure may well be the explanation. Certainly it is asking much of a purely local procedure such as fulguration of the internal sphincter area, the Kelly stitch, or the "direct muscle plastic" of Stoeckel¹⁷ to retain urine which may be at pressures 30 per cent above normal.

(b) The re-establishment of functional urethral resistance has often been lost from view in attempts to re-establish urethral anatomy. Some writers have claimed a constant relationship between incontinence and changes in anatomic

anteroposterior film reveals dilatation for a greater area down the urethra; the oblique view demonstrates more marked funneling and the descent of the bladder floor. Postoperatively, these are corrected in a satisfactory manner by plastic repair, with particular care being taken of the internal sphincter area.

Fig. 16 reveals the type of urethra which has no inherent resistance whatever. Local tightening procedures are of no avail in the face of such complete lack of urethral resistance. Whatever the particular operation selected, it must be one which brings the motive force to the urethra from elsewhere, and this study, therefore, indicates the necessity for some type of transplant operation. This particular patient had a pyramidalis muscle-fascial transplant operation as described by Norman F. Miller,²⁹ and the postoperative films reveal the result. The film shown in Fig. 17 is in marked contrast to the preoperative film, and shows almost complete closure of the urethra. The next x-ray (Fig. 18) was taken immediately after the film shown in Fig. 17, but as this was exposed the patient was asked to raise her head and shoulders from the x-ray table. This action tightened the rectus and pyramidalis muscles, drew tight the fascial sling under the urethra, and the fact that the patient's postoperative continence was based on a new sphincteric action is clearly demonstrated. It should perhaps be re-emphasized that these x-rays are not primarily pictures of structure, but indicate functional ability to resist force applied against the sphincters.

SUMMARY

The difficulty of the accurate evaluation of stress urinary incontinence and the selection of the correct type of operative procedure for any given case is appreciated by all gynecologists. The principles which form the basis for the treatment of this complaint are here presented, and a clinical test is reported which has been used and found satisfactory as indicating the etiology, the operation of choice, and the results of operation for incontinence. It should be emphasized that this test is not intended to replace, but rather to complement, other methods now in use for the evaluation of partial or stress urinary incontinence in women.

REFERENCES

- (1) Bertone, Carlo: *Riforma med.* 52: 973, 1936. (2) Douglass, Marion: *AM. J. OBST. & GYNEC.* 31: 268, 1936. (3) Davies, J. W.: *Surg. Gynec. Obst.* 67: 273, 1938. (4) Frigyesi, Josef: *Arch. f. Gynäk.* 160: 176, 1935. (5) Gomez, Carlos: *J. d'urol.* 45: 344, 1938. (6) Lowsley, O. S.: *J. Urol.* 36: 400, 1936. (7) Millin, T.: *Proc. Royal Soc. Med.* 32: 777, 1939. (8) Muret, M., and Chapin, O. J.: *Gynec. et obst.* 36: 81, 1937. (9) Schrattenbach, V.: *Zentralbl. f. Gynäk.* 61: 1848, 1937. (10) Denny-Brown, D. E., and Robertson, E. G.: *Brain* 56: 149, 1933. (11) Denny-Brown, D. E.: *New England J. Med.* 215: 647, 1936. (12) Davids, A. M., Newman, H. F., and Rubin, I. C.: *J. Mt. Sinai Hosp.* 4: 861, 1938. (13) Young, H.: Quoted by Davids, Newman and Rubin. (14) Rose, D. K.: *J. Urol.* 40: 248, 1938. (15) *Idem*: *Ibid.* 27: 207, 1932. (16) Johnston, H.: *Surg. Gynec. Obst.* 53: 96, 1931. (17) Stoeckel, W.: *Zentralbl. f. Gynäk.* 61: 1224, 1937. (18) Kennedy, W. T.: *AM. J. OBST. & GYNEC.* 34: 576, 1937. (19) Watson, B. P.: *Brit. M. J.* 2: 566, 1929. (20) Thomsen, E.: *Acta radiol.* 13: 433, 1932. (21) Natvig, H.: *Norsk mag. f. laegevidensk.* 92: 325, 1931. (22) Schwartz, O.: *Handbuch der Urologie*, Berlin, 1926. (23) Kennedy, W. T.: *AM. J. OBST. & GYNEC.* 33: 19, 1937. (24) Stevens, W. E., and Smith, S. P.: *J. Urol.* 37: 194, 1937. (25) Miller, J. D.: *Ibid.* 40: 612, 1938. (26) D'Azevedo and Campos: Quoted by Stevens and Smith. (27) Taylor, H., and Watt, C.: *Surg. Gynec. Obst.* 24: 296, 1917. (28) Thomsen, E.: *Acta radiol.* 11: 527, 1930. (29) Miller, Norman F.: *J. A. M. A.* 98: 628, 1932.



Fig. 16.

Fig. 16.—Preoperative view (compare with Fig. 3).

Fig. 17.—Postoperative x-ray, with patient relaxed, shows marked improvement.

Fig. 18.—Postoperative x-ray (with pyramidalis tightened) shows sphincteric action of transplant by increased obliteration of balloon shadow. (See text.)

Fig. 17.

Fig. 18.

interval must elapse between the administration of progesterone and its endogenous production. If progesterone administration is begun during the postmenstrual phase and the treatment then carried on without interruption over the whole of the cycle, no intracyclic bleeding will occur, although a total of 95 or even 105 mg. of progesterone are injected into the organism.

CASE 1.—In this patient, aged 20 years, the menstrual period occurred at a twenty-six-day interval, and bleeding usually persisted for three days. There were no abnormal gynecologic findings. From the fourth day after bleeding had ceased, i.e., the seventh day of the cycle, 5 mg. of progesterone were given intramuscularly daily over a period of nineteen days (95 mg. in all). Bleeding appeared on the expected date of menstruation (twenty-sixth day) and persisted for three days.

CASE 2.—The patient, aged 20 years, had always had normal menstrual periods with bleeding of five to seven days' duration. There were normal gynecologic findings. From the tenth day on, the patient was given 5 mg. of progesterone daily; 105 mg. in all. On the thirtieth day, i.e., on the date of the expected normal menstruation, bleeding set in and persisted for six days. Biopsy performed early during the period of bleeding, revealed that the glands of the uterine mucosa were not overdeveloped, although very large amounts of progesterone had been given. The anatomic picture of the mucous membrane suggested the beginning of the menstrual stage.

II. BLEEDING INDUCED IN SECONDARY AMENORRHEA BY PROGESTERONE ALONE

(a) *The Duration of the Period of Progesterone Administration and Its Influence on the Bleeding Effect.*—After it had been ascertained that it was possible, by five days' administration of 10 mg. of progesterone daily, to produce bleeding in secondary amenorrhea, we tried to shorten the period of hormone administration. Two women, who had been amenorrheic for five months and three years, respectively, were each given a single injection of the whole amount of 50 mg. In neither case did bleeding occur. When, however, this dose was given in two portions on two successive days, bleeding took place (Table I). It is worthy of record that in these cases the

TABLE I. FIFTY MG. OF PROGESTERONE GIVEN ON TWO DAYS IN SECONDARY AMENORRHEA

NO.	NAME	AGE	DURATION OF AMENORRHEA	PROGESTERONE (MG.)	INTERVAL BETWEEN LAST INJECTION AND BLEEDING	DURATION OF BLEEDING
1	K.	18	5 mo.	2 x 25 mg. on two days	72 hr.	3 da.
2	F.	22	3 yr.	2 x 25 mg. on two days	100 hr.	4 da.
3	J.	21	6 yr.	2 x 25 mg. on two days	96 hr.	1 da.

interval between the injection of hormone and the occurrence of bleeding was prolonged. If 50 mg. are distributed over 5 injections, given on five successive days, bleeding usually appears sixty to seventy-two hours after the last hormone injection. If it is, however, given in two portions on two successive days, bleeding does not set in before the lapse of seventy-two to one hundred hours.

(b) *Tabulation of the Cases of Amenorrhea Treated by Progesterone Alone.*—Up to the present, 19 cases of secondary amenorrhea have been treated with progesterone alone. The patients' ages were between 17 and 40 years, and amenorrhea had been present for from four months to seven years. In most of the cases the uterus was found to be hypoplastic. Of the 19 cases, bleeding was induced in 17, which means that in 89.4 per cent the treatment was successful (Table II). The absence of

UTERINE BLEEDING INDUCED BY PROGESTERONE

DURING THE NORMAL MENSTRUAL INTERVAL AND IN AMENORRHEA

BERNHARD ZONDEK, M.D., JERUSALEM, SAMUEL ROZIN, M.D., AND
MORTON VESELL, M.D., NEW YORK, N. Y.

(From the Gynaecological-Obstetrical Department of the Rothschild-Hadassah University Hospital, Jerusalem, and the Endocrine-Clinic of the Beth Israel Hospital, New York)

IN PREVIOUS publications¹ it has been demonstrated that bleeding during the intermenstrual stage can be obtained in the normally menstruating woman by administering 50 mg. of progesterone during the postmenstrual stage, 10 mg. on five successive days. This type of bleeding which occurs from a proliferatively developed mucous membrane (Fig. 1), usually appeared about 60 hours after the last progesterone injection and persisted from three to five days. We termed it "intracyclic bleeding." The patients told us that the general subjective symptoms appearing previous to and during the period of bleeding were much the same as those which occurred from normal menstruation. If, however, progesterone is given during the intermenstrual stage, at a time when the organism has already developed its own corpus luteum, no bleeding occurs. The level of estrone hormone which, under physiologic conditions, is present during the intermenstruum does not prevent the intracyclic bleeding. If, however, additional amounts of estrogenic hormone are given (10 mg. of estradiolbenzoate on four successive days), this will counteract the bleeding effect of progesterone. Pregneninonol per os has the same effect as progesterone parenterally.²

After it had been ascertained that intracyclic bleeding taking place from a proliferatively developed mucous membrane could be induced by progesterone, an attempt was made to use this substance in the treatment of amenorrhoeic women without the preliminary application of estrogens. Seven out of eight cases of secondary amenorrhoea, in which bleeding had been absent from four months to three years, have responded to this treatment. However, we have been unsuccessful with this treatment in five cases of primary amenorrhoea.¹

In the following, we desire to report additional experience with progesterone therapy.*

I. ADMINISTRATION OF PROGESTERONE OVER THE ENTIRE CYCLE

As has been explained above, it is only in certain phases of the cycle that it is possible to induce bleeding with progesterone. If, therefore, a five days' progesterone treatment is begun at the time of follicular rupture no bleeding occurs, since in this case the exogenous administration of corpus luteum hormone coincides with the endogenous production of this factor. The following experiments make it clear that a certain

*Some of the work referred to was done by B. Zondek and M. Vesell in the Beth Israel Hospital in New York.

by giving preliminary treatment with estrogenic hormone, followed by progesterone. Only in very few cases is the cycle re-established in this way. The question now arose as to whether or not the treatment with progesterone alone would be active along those lines. There are as yet only 9 cases at our disposal to report upon since the rest of our patients could not be followed up (Table II). Four of these 9 cases were negative, i.e., only one single period of bleeding occurred after progesterone treatment, and from then on the patient continued to be amenorrheic. In the other 5 cases, however, further cyclic bleeding was induced; in 2 cases the cycle recurred once, in two others twice and in one three times. The latter patient also reported pregnancy.

It was therefore possible to obtain improvement for several months in 50 per cent of the cases of amenorrhea by one series of treatments with progesterone, but even here no permanent success could be achieved.

(d) *Induction of Several Periods of Bleeding After Repeated Administration of Progesterone.*—Up to now it has been assumed that progesterone cannot become active unless it meets a perfectly proliferated mucous membrane, grown under the influence of estrogenic hormone. But the fact that it is possible to induce intracyclic hemorrhages clearly demonstrates that this does not hold true any longer. This means that progesterone is able to induce bleeding even in a mucous membrane which is but imperfectly developed. This is most instructively shown by the following: In secondary amenorrhea bleeding was achieved with 50 mg. of progesterone. After the bleeding had stopped, another course of progesterone was given, following an interval of a few days. This second course of treatment again produced bleeding of several days' duration. In two women we succeeded in producing three successive periods of bleeding by giving three courses of progesterone (Table III).

CASE 1.—F., aged 20 years, had been amenorrheic for five years. Administration of 50 mg. of progesterone, 10 mg. each on five successive days, produced bleeding of three days' duration, after an interval of sixty hours. As early as forty-eight hours after bleeding had stopped another five days' course of progesterone was given, and again bleeding of several days' duration took place.

CASE 2.—K. B., aged 19 years, had been amenorrheic for fourteen months. After five days' treatment with progesterone a period of bleeding of six days' duration occurred after an interval of sixty hours. This time we waited only one day after bleeding had ceased and then began the second course of treatment. After this, bleeding began again, viz., after an interval of seventy hours, and persisted for five days.

TABLE III. SEVERAL PERIODS OF BLEEDING OCCURRING AFTER SEVERAL COURSES OF PROGESTERONE TREATMENT IN SECONDARY AMENORRHEA

NO.	NAME	AGE	DURATION OF AMENORRHEA	UTERINE FINDINGS	PROGESTERONE (MG.)	HOW MANY COURSES OF TREATMENT	HOW MANY PERIODS OF BLEEDING
1	F.	20	5 yr.	Hypoplasia	50 mg. on 5 days	2	2
2	K.B.	19	14 mo.	Hypoplasia	50 mg. on 5 days	2	2
3	L.	40	6 mo.	Normal	50 mg. on 5 days	2	2
4	H.	32	6 mo.		50 mg. on 5 days	2	2
5	K.	26	7 yr.	Hypoplasia	50 mg. on 5 days	3	3
6	K.	19	1 yr.	Hypoplasia	50 mg. on 5 days	3	3

CASE 3.—L., aged 40 years, had been amenorrheic for six months. The development of this case was much the same as that of Case 2. Bleeding occurred after progesterone treatment, then a three days' interval followed, after which a second course of progesterone was given, and again bleeding was obtained.

TABLE II. BLEEDING AND SUBSEQUENT SPONTANEOUS BLEEDING AFTER TREATMENT WITH PROGESTERONE IN SECONDARY AMENORRHEA

NO.	NAME	AGE	DURATION OF AMENORRHEA	UTERINE FINDINGS	PROGESTERONE (MG.)	BLEEDING	SUBSEQUENT SPONTANEOUS BLEEDING
1	J.	21	4 mo.	Normal	5 × 10 mg. on 5 days	+	2 spontaneous periods of bleeding, then amenorrheic again
2	S.	23	6 mo.	Normal	5 × 10 mg. on 5 days	+	None
3	H.	32	6 mo.	Normal	5 × 10 mg. on 5 days	+	
4	L.	40	6 mo.	Normal	5 × 10 mg. on 5 days	+	
5	W.	26	9 mo.	Hypoplasia	5 × 10 mg. on 5 days	+	1 period of bleeding, no further observation
6	F.	24	1 yr.	Normal	5 × 10 mg. on 5 days	+	
7	K.B.	19	1 yr.	Hypoplasia	5 × 10 mg. on 5 days	+	None
8	O.	28	1 yr.	Normal	5 × 10 mg. on 5 days	+	1 spontaneous period of bleeding
9	A.	17	1 yr.	Hypoplasia	5 × 10 mg. on 5 days	+	
10	K.	19	14 mo.	Hypoplasia	5 × 10 mg. on 5 days	+	None
11	M.	37	15 mo.	Normal	5 × 10 mg. on 5 days	+	3 spontaneous periods of bleeding, reports pregnancy
12	D.	19	18 mo.	Hypoplasia	5 × 10 mg. on 5 days	+	
13	G.	21	2 yr.	Hypoplasia neg. vaginal smear	5 × 10 mg. on 5 days	-	
14	D.	23	3 yr.	Normal	5 × 10 mg. on 5 days	+	None
15	F.	18	3 yr.	Hypoplasia	5 × 10 mg. on 5 days	+	
16	F.	20	5 yr.	Hypoplasia	5 × 10 mg. on 5 days	+	
17	K.	26	7 yr.	Hypoplasia	5 × 10 mg. on 5 days	+	
18	G.	40	7 yr.	Highly atrophic	5 × 10 mg. on 5 days	-	
19	K.	26	7 yr.	Hypoplasia	Progestoral tablets 300 mg.	+	2 spontaneous periods of bleeding

estrogen production will probably account for the lack of response in the two other cases. In Case 13 the negative vaginal smear (using the method of Shorr and Papanicolaou) furnished a strong support for this assumption. There were masses of leucocytes and only a few epithelial cells in the smear, similar to that usually found in cases where ovarian function is absent. In Case 18 the uterus was highly atrophic and the patient suffered in addition from hyperthyroidism.

Fig. 2 is an example of a mucous membrane in the proliferative stage found on biopsy in the beginning of the bleeding in an amenorrheic woman following treatment with progesterone alone.

(c) *Permanent Results.*—The therapeutic results obtained up until now in connection with amenorrhea are very unsatisfactory. It is, indeed, possible to induce bleeding in a proliferative mucous membrane with estrogenic hormone, and there is, moreover, the possibility of inducing bleeding in a progestationally converted mucosa

patient with progesterone alone, this is not the case with primary amenorrhea. This led us to conclude that a certain degree of estrogenic hormone production must necessarily be present in the organism should bleeding actually occur. The fact, however, that it was possible, as in our cases of secondary amenorrhea, to induce several periods of bleeding following each other at short intervals suggests that the stimulus exerted by estrogens on the uterine mucosa need only be of the slightest degree. In view of this observation, we tried to stimulate the uterine mucous membrane through a very short preliminary treatment with estradiol benzoate, and then followed with progesterone. Over a period of no more than four days we gave a total of 20,000 I.B.U. of estradiol benzoate whereupon a five days' treatment with progesterone followed.* In those 3 patients who up to the present have been treated in this way, bleeding



Fig. 2.—Photomicrograph of the uterine mucosa taken from a biopsy at the onset of progesterone-induced bleeding in a patient with secondary amenorrhea (fifteen months). The patient received 50 mg. of progesterone in all, administered intramuscularly during five days. At the seventh day bleeding occurred and lasted for three days, from a proliferative endometrium.

was actually obtained. In two further cases we chose another method, giving 20,000 I.B.U. of estradiol benzoate and 50 mg. of progesterone simultaneously, over a period of five days, and here, too, bleeding occurred.

CASE 1.—H., aged 34 years, had never menstruated. When she had undergone laparotomy, the ovaries were also inspected. They were of the size of a cherry, firm, and contained neither follicles nor corpora lutea, strongly resembling, therefore, those usually found in old women. A five days' course of progesterone (50 mg.) which had been given a year before had no effect. Now the patient was given 5,000 I.B.U. of estradiol benzoate daily over a period of four days, totaling 20,000 I.B.U. Then, from the fifth to the ninth day, a total of 50 mg. of progesterone was injected, and from the twelfth to the fifteenth day copious bleeding took place (Fig. 2).

*We are greatly indebted to Roche-Organon Inc., Nutley, N. J., for kindly supplying progesterone (progestin "Roche-Organon") as well as estradiol benzoate (dimenformon benzoate).

CASE 4.—H., aged 32 years, had been amenorrheic for six months. After five days' administration of progesterone, bleeding began. After an interval of six days, another course of progesterone was given and another very copious bleeding occurred.

CASE 5.—K., aged 26 years, had been amenorrheic for seven years. The uterus was 4.5 cm. long and narrow. She was given progesterone over a period of five days (50 mg.). Bleeding took place from the ninth to the twelfth day. After another course of progesterone had been given from the fourteenth to the eighteenth day, bleeding occurred again on the twenty-second day and persisted up to the twenty-fifth day. After an interval of one day, a third course of treatment was given from the twenty-seventh to the thirty-first day, whereupon very copious bleeding occurred a third time on the thirty-fifth day and persisted up to the thirty-eighth day (Fig. 1).

CASE 6.—K., aged 19 years, had been amenorrheic for a year. After five days' treatment with 50 mg. of progesterone, bleeding set in on the eighth day and lasted until the eleventh day. The second course was given from the thirteenth to the seventeenth day and bleeding took place a second time from the twentieth to the twenty-third day. After having waited one day, the third course of progesterone was given from the twenty-fifth to the twenty-ninth day, and on the thirty-second day bleeding occurred a third time and persisted up to the thirty-fifth day.



Fig. 1.—Photomicrograph of the uterine mucosa taken from a biopsy at the onset of intracyclic bleeding in a woman with a normal cycle. The patient had 50 mg. of progesterone in all, administered intramuscularly from the eighth to twelfth day of the cycle. Bleeding occurred on the fourteenth day of the cycle and lasted for three days, from a proliferative endometrium.

From the above we may conclude that, in secondary amenorrhea, it is possible to induce successive periods of bleeding, although there are only very short intermediate periods during which the mucous membrane can be only very slightly developed. No information is, however, as yet available as to how far it may be possible to start the menstrual cycle again by repeated courses of progesterone treatment. This will be reported upon later, when the patients will have been under observation for a greater length of time.

III. BLEEDING IN PRIMARY AMENORRHEA THROUGH PROGESTERONE AND SMALL QUANTITIES OF ESTROGENS

At the beginning of this paper it has been pointed out that, while it is possible to induce bleeding in secondary amenorrhea by treating the

During pregnancy³ even large doses of progesterone (up to 150 mg.) are unable to produce bleeding, and it is, therefore, impossible to induce abortion in this way.

In order that the intracyclic bleeding may take place, a certain interval between exogenous hormone administration and endogenous hormone production is required. If progesterone administration is started at the time of follicular rupture, which means at a stage when progesterone production in the patient's own organism has already begun, no intracyclic bleeding occurs.

Large doses of estrogenic hormone (100,000 I.U. estradiol benzoate, given daily over a period of four days) are active in preventing the intracyclic bleeding and are also able to delay normal menstruation, which must be attributed to impaired gonadotropic secretion in the anterior pituitary lobe (Zondek⁴ 1935/36). Estrogenic hormone must, therefore, be held responsible for three functions: (a) Proliferation of the uterine mucosa, if the amounts administered do not exceed physiologic limits; (b) counteracting the activity of progesterone, if the amounts administered are higher than those physiologically present in the organism; (c) influence on the gonadotropic secretion of the anterior pituitary lobe.

SUMMARY

1. Bleeding of three to five days' duration is induced during the intermenstrual stage by a total of 50 mg. of progesterone given in the postmenstrual stage (intracyclic bleeding).

2. If progesterone is given at the time of follicular rupture, no intracyclic bleeding will occur. There must necessarily be an interval between exogenous progesterone administration and endogenous hormone production. Continuous administration of progesterone over the whole of the cycle produces no intracyclic bleeding either.

3. Pregneninonol per os has the same effect as progesterone given parenterally.

4. It is possible to prevent the occurrence of the intracyclic progesterone-produced bleeding through large doses of estrogenic hormone.

5. In secondary amenorrhea, it is possible to cause bleeding of three to five days' duration by giving a total of 50 mg. of progesterone split up in five doses and given on five successive days; bleeding then appears after an interval of sixty to seventy-two hours.

This bleeding takes place from a proliferatively developed mucous membrane. Seventeen out of 19 cases responded favorably. Instead of five days, 50 mg. of progesterone may also be distributed over two days only; however, if given in one injection, no result is obtained.

6. In roughly 50 per cent of our cases, one course of progesterone was able to improve secondary amenorrhea for several months. Permanent success has not been recorded as yet.

7. After bleeding which has been induced in secondary amenorrhea by progesterone treatment has stopped, another course of progesterone may follow immediately, which, in turn, will also produce bleeding. All

Biopsy on the onset of the bleeding revealed an extremely thin mucosa which contained only few glands in the postmenstrual stage.

CASE 2.—K., aged 30 years, had her ovaries removed. There were serious vasomotor deficiency symptoms. Five days' treatment with progesterone which had been given nine months before, had yielded no result. Now the patient received a total of 20,000 I.B.U. estradiol benzoate over a period of four days and, subsequently, a total of 50 mg. progesterone from the fifth to the ninth day, whereupon, on the twelfth day, bleeding appeared and persisted for three days.

CASE 3.—F., aged 39 years, had never menstruated. She was given 20,000 I.B.U. of estradiol benzoate in all over a period of four days, and, subsequent to this, 50 mg. of progesterone from the fifth to the ninth day. Copious bleeding set in on the twelfth day and persisted up to the fifteenth day.

CASE 4.—K., aged 30 years, had her ovaries removed. This patient was given 4,000 I.B.U. of estradiol benzoate and 10 mg. of progesterone simultaneously daily on five successive days (thus receiving a total of 20,000 I.B.U. of estrone and 50 mg. of progesterone). After the lapse of sixty hours (on the eighth day), bleeding of two days' duration took place.

CASE 5.—H., aged 34 years, had never menstruated. She received 4,000 I.B.U. of estrone and 10 mg. of progesterone simultaneously daily over a period of five days, a total, therefore, of 20,000 I.B.U. of estrone and 50 mg. of progesterone. On the ninth day bleeding of one day's duration appeared.

DISCUSSION

Up to the present it has been assumed that the corpus luteum hormone (progesterone) is only able to produce bleeding of the uterine mucosa, provided that estrogenic hormone has previously been active in bringing about perfect proliferation of the mucous membrane. The present investigations, however, make it clear that it is possible to induce bleeding during the intermenstrual stage (intracyclic bleeding) which takes place from an imperfectly proliferated mucous membrane (as has been verified by biopsy). It is, therefore, no prerequisite for the occurrence of a progesterone-produced bleeding that perfect proliferation be present. These observations were applied in the treatment of amenorrheic women (secondary amenorrhea), and it became evident that to induce bleeding did not require preliminary treatment with estrogens. Seventeen out of 19 cases were successfully treated in this way. It is worthy of record that several periods of bleeding in succession could be induced (e.g., three times during the course of one month) if another course of progesterone was started one to two days after bleeding had stopped. It is, therefore, irrelevant whether the mucous membrane from which bleeding occurs shows only slight or marked proliferation or has even been progestationally converted. The presence of a certain degree of estrogenic hormone production is, as a matter of fact, a prerequisite condition for the appearance of bleeding. Probably, the mucous membrane must be stimulated to a certain extent by this estrone produced in the organism. This is clearly shown by the fact that in primary amenorrhea no result is obtained by treatment with progesterone alone. It is, however, also possible to induce bleeding in primary amenorrhea, provided that small amounts of estrogens are also given, previously to or simultaneously with progesterone.

TABLE I. DATA CONCERNING THE FIVE SUBJECTS

SUBJECTS, HOSPITAL CASE NO.	F-1088	F-1041	A-260	F-795	F-1540
Age	18	17	17	17	17
Height (inches)	?	66	66¼	62	59
Weight in kilograms at onset of experiment	58.1	53.6	74.9	59.5	45.4
Physical condition	Excellent	Excellent	Diabetes Gonorrhea	Syphilis treated	Excellent
No. of previous pregnancies	0	0	0	0	0
Onset last menstrual period	10-8-30	10-7-30	9-16-30	8-9-30	9-10-30
Date of first fetal movements	?	?	February (early)	12-27-30	2-7-31
Health during experiment	Good	Good. Had cold in Feb.	Good	Good	Good
Total gain in weight from first metabolism period until delivery (kilograms)	9.8	17.0	9.8	10.4	10.6
Duration of pregnancy (days)*	291	281	293	280	278
Date of parturition	6-4-31	7-15-31	7-6-31	5-16-31	6-15-31
Character of labor	Low forceps. Pro-lapsed cord	Spontaneous	Spontaneous	Low forceps. Inertia	Spontaneous
Weight of child (grams)	3600	3870	3428	3404	3008
Mother's convalescence	Slightly febrile second to eighth day	Afebrile	Afebrile	Febrile seven-teenth to twenty-second day	Afebrile
Quantity of milk	Stillbirth	Insufficient	Insufficient	Satisfactory	Satisfactory

*Calculated from first day of last menstrual period.

DIET USED

The diets given during the entire period of study were based upon the general prenatal diet* recommended by the Department of Pediatrics, State University of Iowa. Four different arrangements of the recommended foods, Diets A, B, C, and D,† were planned to relieve monotony.

*A minimum of a quart of milk per day; a minimum of one egg; 1 moderate serving of meat or fish; 2 vegetables (one-half cup minimum serving); 2 fruits, 1 of which was served raw (one-half cup minimum serving); 1 teaspoonful cod liver oil; 6 teaspoonfuls butter (one ounce); other foods as bread, cereal, potatoes, were added to satisfy the appetite.

The vegetables were divided into two classes: (1) lettuce, spinach, tomatoes, celery, cauliflower, string beans, asparagus, chard, and cabbage; (2) peas, carrots, beets, turnips, parsnips, onions, rutabagas, eggplant, and squash. Both vegetables might be taken at a serving from class (1) but only one could be taken from class (2).

The fruits from which selections were made were: oranges, grapefruit, apples, peaches, apricots, plums, prunes, pears, and berries. These were either fresh, canned, or dried. Bananas were not served more than twice a week.

†Diets A and B are listed in detailed form as follows (all of the figures are the weight in grams):

Diet A: Breakfast: Cream 75; sugar 20; orange juice 170; butter 10; toast 20; cornflakes 20; egg 50; cocoa made with milk 200, sugar 10, cocoa 5, and several drops of vanilla.

10:00 A.M.: Milk 170; one orange; cod liver oil 6 Gm. followed by 5 Gm. grape juice.

(Continued at bottom of next page.)

6 patients treated in this way showed a satisfactory response. In two of them bleeding was produced three times during the course of one month.

8. Progesterone is able to produce bleeding in an extremely thin mucous membrane which shows only slight evidence of proliferation as well as in the fully developed proliferative one and, likewise, in the pregestational mucous membrane.

9. In primary amenorrhea treatment with progesterone alone fails. Bleeding can, however, be obtained if small amounts of estrogens are also given, either a few days previous to or simultaneously with progesterone.

10. No bleeding is obtained by progesterone treatment during pregnancy.

REFERENCES

- (1) Zondek, B., and Rozin, S.: J. Obst. & Gynaec. Brit. Emp. 45: 919, 1939; 46: 736, 1939. (2) Zondek, B., and Rozin, S.: Lancet 1: 504, 1939. (3) Zondek, B.: See reference 1. (4) Idem: Hormone d. Ovariums u. d. Hypophysenvorderlappens, ed. 2, Julius Springer, Vienna, 1935, pp. 387, 499, 507, and 508; Wien. klin. Wchnschr. 49: 1282, 1936.

CALCIUM, PHOSPHORUS, AND NITROGEN METABOLISM IN WOMEN DURING THE SECOND HALF OF PREGNANCY AND IN EARLY LACTATION*

FRED W. OBERST,† PH.D., LEXINGTON, KY., AND E. D. PLASS, M.D.,
IOWA CITY, IA.

(From the Department of Obstetrics and Gynecology, State University of Iowa,
Iowa City, Iowa)

THE metabolism of calcium, phosphorus, and nitrogen has been studied by a few investigators, but the complicated character of accurate balance experiments has interfered with the accumulation of many data on the various problems involved. This report covers metabolic studies of five pregnant women over some months of gestation, and of three of these patients during the first part of the lactation period. In order to present the data in the most comprehensive form, the results will be reviewed separately.

SUBJECTS

The subjects were 5 young primigravidas admitted to the Obstetric Service especially for this study, and maintained in separate quarters where they were constantly (day and night) under the supervision of a graduate nurse who had no other duties. A certain amount of work was required from each subject to provide sufficient exercise. They also were allowed to spend several hours daily on the hospital roof for fresh air and sunshine. Essential clinical data on each subject are shown in Table I.

*Received for publication, April 6, 1940.

†Now Biological Chemist at the U. S. Public Health Service Hospital.

and its calcium content determined by analysis. The subjects were expected to eat all the food given them, but when any was refused, it was weighed and preserved in 15 per cent sulfuric acid for separate analysis.

During each metabolic period twenty-four-hour urine collections were made. The daily output was thoroughly mixed, measured, and a portion preserved with toluene for analysis. Feces for the entire period, marked by carmine administration at the beginning and end of each period, were collected and preserved in a covered beaker containing 15 per cent sulfuric acid. The breast milk from the subjects, after delivery, was obtained by means of an electric breast pump. One-tenth of each pumping was saved for analysis and the remainder given to the baby, supplemented, when necessary, by formulas. The separate milk specimens were pooled for the entire period and preserved in a refrigerator with a few drops of 30 per cent formalin.

Food, food refusals, and stools, preserved in 15 per cent sulfuric acid, were digested and analyzed according to the methods employed by Stearns.¹ Milk (including breast milk) and cream were analyzed separately, using the same technique. The total nitrogen of the urine was determined by the Kjeldahl method, while the Fiske and Subbarow method² was employed for the inorganic phosphorus. Urine calcium was determined by the method of McCrudden, as modified by Stearns, except that the calcium oxalate was separated by centrifuging rather than by filtering.

FETAL REQUIREMENTS FOR CALCIUM, PHOSPHORUS, AND NITROGEN

So far as the pregnant woman is concerned, the calcium, phosphorus, and nitrogen balances depend upon two factors: (a) the amount needed to supply the demands of the growing fetus and its adnexa, plus the maternal tissue increment and (b) the utilization of these substances ingested. Data on the former factor are available in several reports on mineral analysis of fetuses of different lengths at different periods of intrauterine development: Fehling,³ Hugounenq,⁴ DeLange,⁵ Michel,⁶ Schmitz,⁷ Camerer,⁸ Givens and Macy.⁹ Coons^{10, 11} has made an excellent review of this literature and has prepared tables and charts on mineral requirements for fetal growth.

The various data on fetal analyses for calcium, phosphorus, and nitrogen were combined and graphed against the period of gestation in weeks and the weight of the fetus according to Streeter's¹² tabulation. The average daily increment (in grams) accruing to the fetus in the eighth, ninth, and tenth lunar month is included in Table II.

RESULTS

Calcium.—Ante partum: It is apparent from the figures in Table II that the fetal requirement for calcium increases rapidly in the latter months of gestation, and that there must be a very considerable positive balance in the mother if her fixed stores of calcium are not to be depleted. A number of investigators have reported calcium balances in pregnant women, as summarized in Table II. In a number of these cases, the daily average retention of calcium was evidently not sufficient to meet the fetal requirements.

Each of the four diets had practically the same calcium, phosphorus, and nitrogen content as well as the same caloric value. In determining the amount of food necessary for the subjects, individual variations in size and weight were considered. Diet A was given to the three subjects who weighed from 53 to 59 kilograms at the beginning of the experiment. In this diet the daily intake was approximately as follows: calcium 2.1, phosphorus 1.9, nitrogen 14, fat 168, and carbohydrate 252 Gm., with a total caloric value of approximately 2,954 calories. Another subject, F-1540, weighing 45 kilograms at the beginning of the experiment, received about 10 per cent less food. The diet for the diabetic subject, A-260, weighing 74 kilograms, was arranged to conform with those used in regular diabetic management. It was essentially the same as listed in Diets A, B, C, and D, except there was an increase in fats and a decrease in carbohydrates. Her daily intake, with the exception of the first period, was approximately as follows: calcium 2.5, phosphorus 1.9, nitrogen 15, fat 218, and carbohydrate 172 Gm., with a caloric value of approximately 3,139 calories. The diet given during the first period, having a caloric value of about 2,000 calories and a correspondingly lower calcium, phosphorus, and nitrogen content, proved inadequate to maintain her body weight.

EXPERIMENTAL

The metabolic balances were determined from a ten-day analysis period made once each month. The food was weighed in the diet kitchen and checked by the nurse in charge of the subjects. Diet A was given each day during the ten-day collection period, while Diets B, C, and D were given on successive days between the collection periods to prevent monotony. During the collection periods, an additional serving of Diet A, with the exception of milk and cream, was prepared with each meal and saved for chemical analysis to determine the total intake. This was preserved in a large covered beaker containing sufficient 15 per cent sulfuric acid for its chemical digestion. Since milk from a large dairy herd does not vary appreciably in chemical composition from day to day, only one sample of milk and cream was analyzed during each collection period. Water used by the subjects was carefully measured

Dinner: Milk 200; mashed potatoes 50, with butter 10; butter 10; tomatoes 100, with butter 10; grated beef cake 60, with butter 5; shredded lettuce 40, with mayonnaise 5; bread 20; ice cream 100.

3:00 P.M.: Malted milk consisting of milk 133, ice cream 33, and malt 10.

Supper: Cottage cheese 45, with cream 25; baked potatoes 75, with butter 5; bread 20; butter 10; peas 10, with butter 5; milk 170; canned peaches 120.

8:00 P.M.: Milk 250.

Diet B: Breakfast: Cocoa consisting of milk 200, sugar 10, cocoa 5 and a few drops of vanilla; cream 100; grapefruit sections 100; shredded wheat 20; toast 20; butter 10; egg 50; sugar 10.

10:00 A.M.: Milk 170; one orange.

Dinner: Milk 200; bread 20; butter 10; baked potatoes 50, with butter 10; liver 50, with butter 5; celery 20; sliced apples 50; ice cream 100.

3:00 P.M.: Malted milk consisting of milk 133, ice cream 33, and malt 10.

Supper: Milk 170; bread 20; butter 10; rice 20; sugar 10; string beans 100, with butter 10; deviled egg 50; canned pears 120.

8:00 P.M.: Milk 250.

Diets C and D: These were similar to Diets A and B, the difference being that some of the food products were substituted by a similar product from the recommended list of foods.

TABLE III-A. TEN-DAY CALCIUM BALANCES IN PREGNANT WOMEN
(For daily values divide by 10)

	F-1088	F-1041	A-260	F-795	F-1540	AVE. PER DAY
Fifth Month						
Total intake		21.93				2.19
a. Solid food		5.73				0.58
b. Milk		15.55				1.56
c. Water		0.65				0.06
Total excretion		17.30				1.73
a. Urine		3.58				0.36
b. Feces		13.72				1.37
Retention		4.63				0.46
Sixth Month						
Total intake	21.99	21.13				2.15
a. Solid food	5.59	5.03				0.54
b. Milk	15.55	15.55				1.56
c. Water	0.85	0.55				0.07
Total excretion	17.56	16.08				1.68
a. Urine	5.24	3.73				0.45
b. Feces	12.32	12.35				1.23
Retention	4.33	5.05				0.47
Seventh Month						
Total intake	20.07	21.62	18.59	21.82	16.31	1.97
a. Solid food	4.58	5.34	5.62	5.55	2.98	0.48
b. Milk	14.68	15.55	11.70	15.30	12.84	1.40
c. Water	0.81	0.73	1.27	0.97	0.49	0.085
Total excretion	15.33	12.83	16.27	16.91	10.96	1.45
a. Urine	5.43	3.88	2.67	1.35	1.35	0.29
b. Feces	9.90	8.95	13.60	15.56	9.16	1.14
Retention	4.74	8.79	2.32	4.91	5.35	0.52
Eighth Month						
Total intake	21.81	21.05	25.63	20.46	19.23	2.16
a. Solid food	5.34	4.64	7.06	5.01	3.90	0.52
b. Milk	15.55	15.55	17.42	14.38	14.00	1.54
c. Water	0.92	0.86	1.15	1.07	1.33	0.11
Total excretion	14.15	15.13	18.89	16.69	14.63	1.59
a. Urine	5.26	4.18	2.89	1.54	1.73	0.31
b. Feces	8.89	10.95	16.00	15.15	12.90	1.28
Retention	7.66	5.92	6.74	3.77	4.60	0.57
Ninth Month						
Total intake	21.23	20.77	24.96	22.45	19.05	2.17
a. Solid food	4.64	4.44	6.80	5.34	3.32	0.49
b. Milk	15.55	15.55	17.42	15.55	14.00	1.56
c. Water	1.04	0.78	0.74	1.56	1.73	0.12
Total excretion	14.30	14.01	16.37	16.23	12.99	1.48
a. Urine	4.60	3.64	3.37	1.77	1.14	0.29
b. Feces	9.70	10.37	13.00	14.46	11.85	1.19
Retention	6.93	6.76	8.59	6.22	6.06	0.69
Tenth Month						
Total intake			26.39	21.84	19.97	2.27
a. Solid food			7.30	4.64	4.36	0.54
b. Milk			17.42	15.56	14.00	1.57
c. Water			1.67	1.64	1.61	0.16
Total excretion			18.62	17.12	14.35	1.67
a. Urine			2.12	1.66	0.35	0.14
b. Feces			16.50	15.46	14.00	1.53
Retention			7.77	4.72	5.62	0.60

TABLE II. SUMMARY OF CALCIUM, PHOSPHORUS, AND NITROGEN BALANCE STUDIES. DAILY AVERAGE BALANCE (GRAMS)

INVESTIGATORS	NO. OF SUBJECTS	NO. OF PERIODS	CALCIUM		PHOSPHORUS		NITROGEN		REMARKS
			INTAKE	RETENTION	INTAKE	RETENTION	INTAKE	RETENTION	
Zacharjewsky ²³	6	6					11.55-24.08	0.95-5.37	Limited diet
Schrader ²⁴	2	2					22.20-22.54	5.97-6.75	Completed diet
Slemons ²⁵	4	4					13.80-16.77	0.42-4.72	Completed diet
Hahl ²⁶	2	7					15.89-20.79	0.60-4.11	
Bar and Daunay ²¹	3	11*					13.71-21.66	5.10-10.97	
Hofström ¹³	1	23	1.01-2.39	-0.33-0.95	2.75-4.30	-0.29-1.14	7.15-17.46	-1.21-3.53	Continuous observation
Landsberg ²²	6	8†			1.15-2.86	-0.15-0.59	12.03-18.90	1.38-3.94	Periodic type of balance
Landsberg ¹⁴	14	14	1.82-2.94	0.02-0.83	1.77-1.94	0.23-0.36	12.21-16.10	0.05-2.98	Self-chosen diet
Wilson ²⁷	3	37			2.19-3.10	0.10-1.27	7.88-19.72	0.46-6.37	Continuous observation
Coons-Blunt ¹⁵	9	23	0.60-1.62	-0.11-0.29	0.94-2.21	-0.14-0.53	7.74-14.31	-0.43-8.45	Home diet
Sandiford et al. ²⁸	1	5					11.20-14.92	-1.90-1.10	Computed diet
Macy et al. ¹⁶	3	12	1.53-2.69	-1.28-0.28	1.46-2.97	-0.16-0.53			Ordinary diet
Macy et al. ¹⁷	1	2	1.55-1.93	0.62-0.64	1.76-1.99	0.17-0.39	11.50-12.20	2.20-2.90	Specified diet
Toverud ¹⁸	16	27	0.58-1.69	-0.43-0.68	0.71-1.98	-0.61-0.74			Ordinary diet
Toverud ¹⁸	23	30	0.81-2.16	0.26-0.90	0.71-2.63	-0.35-1.14			Regulated diet
Coons ¹⁰	6	25	0.81-2.38	0.06-0.45	1.05-2.56	0.03-0.77	8.08-19.13	0.49-5.20	Home diet
Hunscher et al. ²⁹	3	12					11.58-23.58	-0.67-6.25	
This study	5	21	1.63-2.64	0.23-0.88	1.44-2.00	0.02-0.68	9.99-15.15	-0.77-3.65	Regulated diet
Daily amounts deposited in fetus during eighth, ninth, and tenth month, respectively, of intrauterine growth.			0.10, 0.25,	0.29	0.04, 0.16,	0.17	0.43, 0.62,	0.97	

*3 for nitrogen.

†13 for nitrogen.

TABLE IV-A. TEN-DAY PHOSPHORUS BALANCES IN PREGNANT WOMEN

(For daily average divide by 10)

	F-1088	F-1041	A-260	F-795	F-1540	AVE. PER DAY
Fifth Month:						
Total intake		20.25				2.03
a. Solid food		8.63				0.86
b. Milk		11.62				1.16
Total excretion		15.24				1.52
a. Urine		9.73				0.97
b. Feces		5.51				0.55
Retention		5.05				0.51
Sixth Month:						
Total intake	19.89	19.91				1.98
a. Solid food	8.27	8.29				0.85
b. Milk	11.62	11.62				1.16
Total excretion	14.79	13.12				1.40
a. Urine	10.64	7.44				0.90
b. Feces	4.15	5.68				0.49
Retention	4.90	6.79				0.58
Seventh Month:						
Total intake	18.45	19.32	14.57	19.66	14.41	1.73
a. Solid food	7.48	7.70	5.94	8.23	4.81	0.68
b. Milk	10.97	11.62	8.63	11.43	9.60	1.05
Total excretion	12.15	15.16	14.35	14.94	13.36	1.40
a. Urine	8.64	10.13	9.43	9.42	7.06	0.89
b. Feces	3.51	5.03	4.92	5.52	6.30	0.51
Retention	6.30	4.16	0.22	4.72	1.05	0.33
Eighth Month:						
Total intake	19.32	19.27	19.51	18.91	17.46	1.89
a. Solid food	7.70	7.65	6.66	8.16	7.02	0.75
b. Milk	11.62	11.62	12.85	10.75	10.44	1.15
Total excretion	12.97	16.25	16.27	15.24	14.08	1.50
a. Urine	9.57	12.01	11.42	9.39	9.18	1.03
b. Feces	3.40	4.24	4.85	5.85	4.90	0.46
Retention	6.35	3.02	3.24	3.67	3.38	0.39
Ninth Month:						
Total intake	19.27	18.91	19.85	19.32	17.65	1.90
a. Solid food	7.65	7.29	7.00	7.70	7.21	0.74
b. Milk	11.62	11.62	12.85	11.62	10.44	1.16
Total excretion	15.04	15.20	15.24	15.59	14.08	1.50
a. Urine	11.42	10.92	11.91	10.14	9.01	1.07
b. Feces	3.62	4.28	3.33	5.45	5.07	0.44
Retention	4.23	3.71	4.61	3.73	3.57	0.40
Tenth Month:						
Total intake			19.55	19.28	17.48	1.88
a. Solid food			6.70	7.66	7.04	0.71
b. Milk			12.85	11.62	10.44	1.16
Total excretion			15.26	16.78	13.21	1.51
a. Urine			11.05	11.04	8.02	1.00
b. Feces			4.21	5.74	5.19	0.50
Retention			4.29	2.50	4.27	0.37

from 1.44 to 2.0 Gm. and the retention from 0.022 to 0.68 Gm. The lowest figure (0.022 Gm. per day retention) occurred in subject A-260, who was the largest woman of the group and did not receive sufficient food during that period to maintain her body weight. The amount was increased considerably the following month, so that the phosphorus intake was increased from 1.46 to 1.95 Gm. per day, and the retention rose from 0.02 to 0.32 Gm. In all of the other metabolic periods, the amount of phosphorus retained exceeded the amount needed for fetal development.

The data on 21 ten-day metabolic study periods on calcium intake (solid food, milk, and water), output (feces and urine), and retention in 5 pregnant women from the fifth through the tenth month of gestation are presented. The daily intake for the subjects ranged from 1.63 to 2.64 Gm. and the retention from 0.23 to 0.88 Gm. In every case the calcium retention exceeded the required calcium deposition of the fetus. The lowest daily retention (0.23 Gm.) occurred in one individual during the seventh month when the fetal calcium requirement was still at a low level.

Post partum: Hunscher²⁰ has made calcium balance studies on 3 women in early lactation and found a negative calcium balance in spite of the high calcium intake. Macy and others,¹⁹ in similar studies on 3 nursing mothers before and after supplementing their customary home diets with cod-liver oil and yeast, found that daily feedings of 15 Gm. of cod-liver oil and 10 Gm. of yeast over a period of two months, when the milk flow persisted at its maximum, stimulated better calcium and phosphorus utilization in all 3 patients.

The intake in 4 metabolic studies in early lactation varied from 1.92 to 2.18 Gm. and the retention from 0.024 to 0.511 Gm. per day. The retentions in subject F-795 were 0.07 Gm. per day in the first month after delivery and 0.02 in the second month. Her milk flow, however, was unusually good which undoubtedly

TABLE III-B. TEN-DAY CALCIUM BALANCES IN POST-PARTUM WOMEN
(For daily values divide by 10)

	A-260	F-795	F-1540
First Month	During the third week after delivery	During the first and second weeks after delivery	During the first and second weeks after delivery
Total intake	21.08	19.21	19.43
a. Solid food	4.58	3.23	4.61
b. Milk	16.50	14.59	13.61
c. Water	----	1.39	1.21
Total excretion	15.97	18.52	15.15
a. Urine	0.85	1.24	1.12
b. Feces	14.20	13.45	13.60
c. Breast milk	0.92	3.83	0.43
Retention	5.11	0.69	5.01
Second Month		During the fifth and sixth weeks after delivery	
Total intake		21.84	
a. Solid food		4.85	
b. Milk		15.55	
c. Water		1.44	
Total excretion		21.60	
a. Urine		2.70	
b. Feces		16.66	
c. Breast milk		2.24	
Retention		0.24	

accounted for these low values. The retentions of calcium in the other two subjects during the first month after delivery were much higher, being 0.51 and 0.50 Gm. per day, respectively. The quantity of milk secreted by them was, however, very much limited.

Phosphorus.—Ante partum: A summary of the literature on phosphorus balance studies in pregnant women is given in Table II. The daily phosphorus intakes and retentions among these subjects are quite variable. A number of them did not retain sufficient phosphorus for the fetal demand.

The detailed data concerning the phosphorus balances for our 5 subjects during 21 metabolic periods are presented in Table IV-A. The total daily intake ranged

TABLE V-A. TEN-DAY NITROGEN BALANCES IN PREGNANT WOMEN

(For daily average divide by 10)

	F-1088	F-1041	A-260	F-795	F-1540	AVE. PER DAY
Fifth Month						
Total intake		146.32				14.63
a. Solid food		84.49				8.45
b. Milk		61.83				6.18
Total excretion		109.85				10.99
a. Urine		98.01				9.80
b. Feces		11.84				1.18
Retention		36.47				3.65
Sixth Month						
Total intake	143.38	148.48				14.59
a. Solid food	81.55	86.65				8.41
b. Milk	61.83	61.83				6.18
Total excretion	109.69	114.72				11.22
a. Urine	98.29	103.60				10.09
b. Feces	11.40	11.12				1.13
Retention	33.69	33.76				3.37
Seventh Month						
Total intake	138.38	143.13	116.15	140.87	99.90	12.77
a. Solid food	80.01	81.30	69.80	80.05	48.84	7.20
b. Milk	58.37	61.83	46.35	60.82	51.06	5.57
Total excretion	114.10	113.77	112.00	112.99	96.65	10.99
a. Urine	102.80	102.74	103.21	98.98	79.27	9.74
b. Feces	11.30	11.03	8.79	14.01	17.38	1.25
Retention	24.28	29.36	4.15	27.87	3.25	1.78
Eighth Month						
Total intake	143.13	142.29	151.50	143.68	131.17	14.22
a. Solid food	81.30	80.46	82.50	86.53	75.50	8.13
b. Milk	61.83	61.83	69.00	57.15	55.67	6.11
Total excretion	109.27	126.28	133.51	113.69	138.85	12.43
a. Urine	96.00	114.92	121.53	99.11	126.32	11.16
b. Feces	13.27	11.36	11.98	14.58	12.53	1.27
Retention	33.86	16.01	17.99	29.99	-7.68*	2.42
Ninth Month						
Total intake	142.29	137.08	151.40	143.13	129.87	14.07
a. Solid food	80.46	75.25	82.40	81.30	74.20	7.87
b. Milk	61.83	61.83	69.00	61.83	55.67	6.20
Total excretion	121.63	118.03	122.71	118.18	110.32	11.82
a. Urine	108.23	108.35	110.85	104.40	97.60	10.59
b. Feces	13.40	9.68	11.86	13.78	12.72	1.23
Retention	20.66	19.05	28.69	24.95	19.55	2.26
Tenth Month						
Total intake			144.30	142.32	129.74	13.88
a. Solid food			75.30	80.50	74.07	7.66
b. Milk			69.00	61.82	55.67	6.22
Total excretion			127.33	133.86	112.82	12.47
a. Urine			111.65	119.70	99.76	11.04
b. Feces			15.68	14.16	13.06	1.43
Retention			16.97	8.46	16.92	1.41

*Not included in average per day.

offered. The retentions for the various metabolic periods are inexplicably variable, but in all but two instances the nitrogen retention exceeded the amount required for fetal growth, and may be assumed to have been sufficient for the maternal growth incident to pregnancy.

Post partum: Slemmons,²⁵ Hahl,²⁶ Harding and Montgomery,³⁰ and Macy and others,¹⁹ found that nitrogen balances usually were negative in the puerperium in spite of generous nitrogen intakes.

Post partum: Hunscher²⁰ has recorded observations on the phosphorus balance of 3 women in successive lactation periods. These women who had a number of previous pregnancies with prolonged and abundant flow of milk were in negative phosphorus balance from the sixth to the twenty-seventh weeks of lactation, even though they were receiving diets containing as much as 3 to 4 Gm. of phosphorus per day. Macy and others¹⁹ also reported phosphorus balances on three nursing mothers before and after supplementing their customary home diets with cod-liver oil and yeast, which stimulated phosphorus utilization.

In the present report 4 ten-day phosphorus balance studies as early as the first and second weeks after delivery are given.

TABLE IV-B. TEN-DAY PHOSPHORUS BALANCES IN POST-PARTUM WOMEN
(For daily average, divide by 10)

	A-260	F-795	F-1540
First Month	During the third week after delivery	During the first and second weeks after delivery	During the first and second weeks after delivery
Total intake	18.94	17.01	15.90
a. Solid food	7.24	6.07	5.75
b. Milk	11.70	10.94	10.15
Total excretion	17.82	18.85	16.15
a. Urine	12.00	11.82	10.17
b. Feces	5.26	5.22	5.36
c. Breast Milk	0.56	1.81	0.62
Retention	1.12	-1.84	-0.25
Second Month		During the fifth and sixth weeks after delivery	
Total intake		19.53	
a. Solid food		7.91	
b. Milk		11.62	
Total excretion		17.42	
a. Urine		10.89	
b. Feces		5.54	
c. Breast Milk		0.99	
Retention		2.11	

In the first month after delivery one patient, A-260, showed a retention of 0.11 Gm. on a daily intake of 1.89 Gm. Her milk flow was not very strong and the phosphorus in the excreted milk averaged only 0.056 Gm. per day for the ten-day period. The other two patients, who produced larger quantities of milk, were in negative balance.

A second study was made during the second month after delivery on one of the subjects (F-795) who in the first month had been in negative balance. The phosphorus intake was increased from 1.70 to 1.95 Gm. per day, while the milk flow had diminished so that the amount of phosphorus in the milk decreased from 0.18 to 0.10 Gm. per day. The phosphorus retention was 0.21 Gm. per day in contrast to the negative balance during the first and second weeks after delivery.

Nitrogen.—Ante partum: A number of investigators have studied nitrogen balances in the latter part of gestation as summarized in Table II. It is apparent that an average woman on an adequate diet, containing at least 7.7 Gm. of nitrogen per day, will store nitrogen. This amount, however, may vary considerably among different individuals. The fetus and its adnexa as well as the maternal tissue increment require large amounts of nitrogen to maintain a positive nitrogen balance.

In the present study of the 21 balances from the fifth through the tenth month of gestation, the daily nitrogen intake ranged from 9.99 to 15.15 Gm. and the retention from -0.77 to 3.65 Gm. Subject F-1540 was in negative nitrogen balance during one of the metabolic periods, even though she consumed most of the food

In addition to the acid-base properties of food elements, Macy and others found that sufficient amounts of vitamins C and D and of ultraviolet light or sunshine were necessary for adequate calcium and phosphorus retention during pregnancy and lactation. Moreover, the best retention of these substances was obtained when the calcium-phosphorus ratio of the food was between 1.0 and 1.5, as a relative excess of either element tended to depress the retention of both. In this study the calcium-phosphorus ratio of the food was within these limits. Each woman in the present series received 6 Gm. of cod-liver oil followed by 5 Gm. of grape juice daily in addition to the fruit in the diet, which supplied considerable amounts of vitamins C and D. They were also exposed to a variable amount of sunshine. One subject, F-1540, who was ill part of the time during the first two metabolism periods, had a low retention of calcium, phosphorus, and nitrogen, but after she was given daily ten-minute ultraviolet radiations for about a month, the retentions were improved to the level of the other subjects.

Little is known regarding the factors affecting dental conditions in pregnancy.

Hanke³² has stated that "The prevalence of dental caries during puberty and pregnancy is well recognized. The underlying predisposing factors in dental caries appear to be metabolic, and I believe that improper diet is the commonest predisposing factor in all dental conditions." At best, our knowledge regarding the role of nutrition in tooth formation and preservation in the life cycle of an individual is not well understood. The majority of dental surgeons and obstetricians believe that the incidence of dental caries is higher in pregnant than in nonpregnant women, living under similar dietary conditions. Among the 9 women studied by Coons and Blunt¹⁵ only 3 were storing as much calcium as was demanded by the fetus. Associated with these low calcium retentions, there was evidence of maternal tooth decay and of poor bone formation, as determined by x-ray examinations on the eighth day after birth.

Throughout the present metabolic studies, the condition of the teeth was carefully observed since each subject had caries on admission. Periodic examinations of the teeth were made by a dental surgeon, the results of which have previously been reported.³³ All cavities originally recorded were left untouched and open to all extraneous influences; no dental restorative work was done. In no case did new dental caries develop. In one case there was complete arrest of decay for the period of the study, and a consistent improvement in the teeth of all subjects was noted over the entire period of observation.

It is well recognized by various investigators that numerous factors are involved in the storage of nitrogen in pregnant women. In addition to the nitrogen requirements of the fetus, it is necessary to consider the amounts required by the placenta, amniotic fluid, and maternal tissue gain. Furthermore, such factors as the nutritive state of the woman before pregnancy, the accustomed level of protein intake, the quality of protein, and the calorie intake in the form of carbohydrates and fats influence the basal requirements for maternal nitrogen storage. A review of the studies reported in the literature indicates that it is impossible to state the protein requirements of the pregnant woman except

The total daily intake in the present study on 4 ten-day metabolic balances ranged from 11.6 to 16.8 Gm. The two subjects studied during the first and second weeks of the puerperium were in negative balance, whereas those investigated in the third, and in the fifth and sixth weeks after delivery were decidedly in positive balance.

TABLE V-B. TEN-DAY NITROGEN BALANCES IN POST-PARTUM WOMEN
(For daily average divide by 10)

	A-260	F-795	F-1540
First Month	During the Third Week After Delivery	During the First and Second Weeks After Delivery	During the First and Second Weeks After Delivery
Total intake	167.50	119.16	116.20
a. Solid food	99.40	60.98	62.09
b. Milk	68.10	58.18	54.11
Total excretion	156.70	130.77	138.79
a. Urine	141.10	112.91	116.24
b. Feces	10.10	15.12	15.58
c. Breast milk	5.50	2.74	6.97
Retention	10.80	-11.61	-22.59
Second Month		During the Fifth and Sixth Weeks After Delivery	
Total intake		152.19	
a. Solid food		90.36	
b. Milk		61.83	
Total excretion		122.12	
a. Urine		92.80	
b. Feces		15.82	
c. Breast milk		13.50	
Retention		30.07	

DISCUSSION

Pregnancy.—It was the purpose of this study to determine the calcium, phosphorus, and nitrogen metabolism in pregnant women under dietary conditions which, at the present time, are believed to be nearly ideal for the growth and development of the fetus without depleting the maternal organism of these elements. Coons¹⁰ has made an excellent study of this subject and has presented a thorough review of the factors involved in the retention of these dietary constituents. Because the products of conception cause notable readjustments in the physiologic processes of the maternal organism, the pregnant woman is subjected to unaccustomed nutritional requirements for fetal growth, for the preparation of her own body tissues for parturition, and for the future elaboration of milk.

The most important factors in the utilization of calcium and phosphorus by man have been reviewed by Macy, Hunscher, McCosh, and Nims.¹⁹ They believe that, even though the mineral intake may be adequate, the acid-base equilibrium of the body and the acid-base properties of the food play an important role in calcium excretion, and will determine the extent of retention. Shohl²¹ has pointed out that an alkaline diet is strongly indicated for the best calcium and phosphorus utilization during pregnancy and lactation. The diet used in the present study was decidedly on the alkaline side, the amounts of basic constituents being about three times the acid constituents. The results, therefore, appear to support the contentions of Shohl.

retention may be stored in the trabeculae of the bones^{35, 36} as a labile reserve supply which can be utilized during lactation. Hence, the better the storage of calcium, phosphorus, and nitrogen during gestation, the greater the reserve for lactation.

SUMMARY

1. A series of 21 ten-day calcium, phosphorus, and nitrogen balance experiments were made on 5 women between the twenty-first and the fortieth weeks of pregnancy. Three of these women were also studied during early lactation.

2. The experiments were planned to obtain the maximum retention of calcium, phosphorus, and nitrogen during pregnancy. The results indicate that this end was accomplished.

3. The daily calcium intake for the various subjects during pregnancy ranged from 1.63 to 2.64 Gm. and the daily retention from 0.23 to 0.88 Gm.

4. The calcium intake in 4 metabolic balances during lactation varied from 1.92 to 2.18 Gm. with retentions varying from 0.02 to 0.51 Gm. per day. The subjects with the highest milk excretion had the lowest retention.

5. The daily phosphorus intakes during pregnancy ranged from 1.44 to 2.0 with retentions from 0.022 to 0.68 Gm.

6. The daily phosphorus intakes in four periods during early lactation on three women ranged from 1.59 to 1.95 and the retentions from -0.18 to 0.21 Gm. The negative balances shown by two women occurred shortly after parturition.

7. The daily nitrogen intakes in 5 pregnant women ranged from 9.99 to 15.15 with retentions from -0.77 to 3.65 Gm. The negative balance appeared in a subject who was ill during the collection period.

8. The total nitrogen intake during early lactation ranged from 11.6 to 16.8 Gm. per day. Two ten-day collection periods during the first and second weeks of the puerperium gave negative balances. Two other periods, one in the third and one in the fifth and sixth weeks of the puerperium, showed definitely positive balances.

REFERENCES

- (1) *Sterns, Genevieve*: J. Lab. & Clin. Med. 14: 954, 1929. (2) *Fiske, C. H., and Subbarow, F.*: J. Biol. Chem. 66: 375, 1925. (3) *Fehling, H.*: Arch. f. Gynäk. 11: 523, 1877. (4) *Hugounenq, L.*: J. de physiol. et de path. gén. 2: 509, 1900. (5) *DeLange, C.*: Ztschr. f. Biol. 40: 526, 1900. (6) *Michel, C.*: Compt. rend. Soc. de Biol. 51: 422, 1899. (7) *Schmitz, E.*: Arch. f. Gynäk. 121: 1, 1923. (8) *Camerer, W.*: Ztschr. f. Biol. 43: 1, 1902. (9) *Givens, M. H., and Macy, I. G.*: J. Biol. Chem. 102: 7, 1933. (10) *Coons, C. M.*: Okla. Agri. Exper. Sta. Bull., No. 223, 1935. (11) *Coons, C. M.*: Thesis, Univ. of Chicago, p. 6, 1929. (12) *Streeter, G. L.*: Contrib. Embryol. (Carnegie Inst.), Wash. 11: 143, 1920. (13) *Hoffström, K. A.*: Skandinav. Arch. f. Physiol. 23: 327, 1910. (14) *Landsberg, E.*: Ztschr. f. Geburtsh. u. Gynäk. 76: 53, 1914. (15) *Coons, C. M., and Blunt, K.*: J. Biol. Chem. 86: 1, 1930. (16) *Macy, I. G., Hunscher, H. A., Nims, B., and McCosh, S. S.*: J. Biol. Chem. 86: 17, 1930. (17) *Macy, I. G., Donelson, E., Long, M. L., and Graham, A.*: J. Am. Dietet. A. 6: 314, 1931. (18) *Toverud, K. U., and Toverud, G.*: Norsk. mag. f. laegevidensk. 90: 1245, 1929; 91: 53 and

within very wide limits. Our women with a protein intake ranging from 11 to 15 Gm. of nitrogen per day met their own protein requirements satisfactorily.

In an average diet approximately two-thirds to three-fourths of the calcium, over half of the phosphorus, and nearly half of the nitrogen intake is from milk or milk products. The importance of using large quantities of milk and certain of its prepared products during pregnancy can not be overemphasized. Certainly no other single food substance will supply these dietary constituents as abundantly as milk.

Lactation.—In addition to the maintenance of her own tissue, a lactating woman requires minerals for secretion in the milk. The minerals may be supplied from her food or from her own mineral reserve. The occurrence of osteomalacia in cows, goats, rats, and women after repeated pregnancies associated with negative calcium and phosphorus balances indicates that calcium must be withdrawn from the maternal organism under such adverse conditions. The quantity of minerals excreted in the milk will depend largely on the volume of milk produced, since the mineral concentration of the milk tends to remain fairly constant. The mineral demands for the production of milk alone may be equal to that required for maternal maintenance. The lactation requirements of one woman may be two or three times greater than those of another woman who is producing smaller quantities of milk. Macy, Hunscher, McCosh, and Nims,¹⁹ reported that daily feedings of cod-liver oil and yeast stimulated better calcium and phosphorus utilization. The fecal excretion of both calcium and phosphorus was decreased, indicating a marked alteration in metabolism and accounting for the greater assimilation of these elements.

In the present study the same diet prescribed during pregnancy was used during the lactation period. Cod-liver oil was included as usual, but not yeast. These experiments were not continued long enough during the puerperium really to test the adequacy of the diet for lactation. It is, however, believed that the prescribed general diet used during pregnancy would be quite satisfactory for milk production, since there was a definite retention of calcium in all of the post-partum experiments. Moreover, in two of the periods both the phosphorus and nitrogen balances were positive. It is known to be difficult to maintain a woman in positive calcium, phosphorus, and nitrogen balance during the first few weeks after delivery.

It is believed that the pregnant woman on an adequate diet stores nitrogen in excess of the amount needed for the fetus, its adnexa, and the normal growth of the maternal reproductive organs. It has been pointed out by Harding³⁴ that at least a part of this excess protein is deposited as a labile reserve against the demands of lactation. However, not all of the labile nitrogen is available for milk formation, since immediately following parturition there is a marked nitrogen loss associated with involution of the uterus.

It has been demonstrated that the pregnant woman on a satisfactory diet will store calcium and phosphorus in excess of the fetal needs. It is believed that a significant portion of the calcium and phosphorus

vertibility into thrombin are both measured. This test gives a good clinical index of the tendency of the patient to bleed.

In the work which we are reporting we used a slight modification of the simplified bedside technique of Smith, Ziffren, Owen and Hoffman.

Briefly, the technique which we employed is as follows:

Fresh rabbit's brain is extracted with acetone until a fine powder is obtained as described by Quick.²⁸ It is then dried in the incubator, sealed in glass tubes, and stored in the icebox until needed. To make the thromboplastin, one-tenth of a gram of the dried brain is added to about 10 c.c. of normal saline and incubated for forty-five minutes. The mixture is then centrifuged at low speed, and the supernatant fluid is poured off. One-tenth cubic centimeter of thromboplastin thus obtained is placed in a small serologic tube, and enough fresh blood is added to make 1 c.c. The tube is then at once inverted over the finger to obtain complete mixing, and then tilted back and forth until clotting occurs. The time is carefully measured with a stop watch. The normal is determined each day. The calculation is then made by the equation,

$$\frac{\text{Clotting activity}}{(\text{in \% of normal})} \text{ equals } \frac{\text{Clotting time of normal}}{\text{Clotting time of patient's blood}} \times 100\%.$$

If the patient's blood clots in fifty seconds and normal is twenty-five seconds, the clotting activity will be 50 per cent. Expressed in the equation it will be,

$$\text{Clotting activity equals } \frac{25}{50} \times 100 \text{ per cent equals } 50 \text{ per cent.}$$

A two-stage titration technique was used in the early experiments of Brinkhous, Smith and Warner,^{29, 30} in which they reported plasma prothrombin level in young infants as less than half as high as in normal adults. In this early work they obtained 14 to 39 per cent of normal.

Quick and Grossman,³¹ using the Quick method, reported a series of cases in the proceedings of the Society of Experimental Biology and Medicine, 1939, in which blood was obtained by venipuncture from healthy infants 3 to 7 days old, and their results showed that the prothrombin concentrations were essentially the same as for normal adults. Also, in an article published in January of this year, Quick and Grossman,³² using the Quick method, report the concentration of prothrombin in cord blood of normal infants as 60 to 70 per cent of normal adult blood. Shortly after birth they showed there is a drop in the prothrombin level, and it may reach very low levels, but tends to return spontaneously to normal between the fifth and seventh day.

Waddell and Guerry²³ reported a series of 20 infants, in which they kept 10 as controls, and gave K orally to 10. They gave 1 c.c. on the first day of life and 0.5 c.c. on the second and third days. They used Quick's method of prothrombin determination and showed that the highest clotting times occurred between forty-eight and seventy-two hours after birth, thus showing a low prothrombin level at this time. There was considerably less individual variation in the clotting times of the infants receiving vitamin K, and the clotting time in this group tended to maintain a common level. Dam, Tage-Hansen and Plum³³ report a similar series in the December, 1939, *Lancet*, arriving at the same conclusions.

Hellman, Delfs, and Shettles^{34, 35} from Johns Hopkins have reported low prothrombin levels in 31 full-term normal infants and 17 premature infants. The prematures in their series were considerably lower than the full terms. They gave 4,500 Almqvist units of vitamin K each day to five mothers from fourteen to thirty-five days before delivery, and raised the prothrombin level markedly in both the mother and infant. They also succeeded in raising the mothers' and babies' levels by giving single doses of the vitamin during labor. These workers used cord blood for their determinations. Our results differ from theirs in that they obtained much lower levels in the untreated infants' cord blood than we observed. These workers used the two-stage technique in their observations.

286, 1930; 92: 677, 1931; *Acta paediat.* 12: Supplementum 2, 28, 1931. (19) Macy, I. G., Hunscher, H. A., McCosh, S. S., and Nims, B.: *J. Biol. Chem.* 86: 59, 1930. (20) Hunscher, H. A.: *J. Biol. Chem.* 86: 37, 1930. (21) Bar, P., and Daunay, R.: *J. de physiol. et de path. gén.* 7: 832, 1905. (22) Landsberg, E.: *Ztschr. Geburtsh. u. Gynäk.* 71: 163, 1912. (23) Zacharjewsky, A. U.: *Ztschr. f. Biol.* 30: 368, 1894. (24) Schrader, T.: *Arch. f. Gynäk.* 60: 534, 1900. (25) Slemons, J. M.: *Johns Hopkins Hosp. Reports* 12: 111, 1904. (26) Hahl, C.: *Arch. f. Gynäk.* 75: 31, 1905. (27) Wilson, K. M.: *Bull. Johns Hopkins Hosp.* 27: 121, 1916. (28) Sandiford, I., Wheeler, T., and Boothby, W. M.: *Am. J. Physiol.* 96: 191, 1931. (29) Hunscher, H. A., Donelson, E., Nims, B., Kenyon, F., and Macy, I. G.: *J. Biol. Chem.* 99: 507, 1933. (30) Harding, V. J., and Montgomery, R. C.: *Ibid.* 73: 27, 1927. (31) Shohl, A. T.: *Physiol. Rev.* 3: 509, 1923. (32) Hanke, M. T.: *J. Am. Dent. A.* 16: 2263, 1929. (33) Drain, C. L., Plass, E. D., and Oberst, F. W.: *Abst. in J. Dent. Research* 13: 233, 1933. (34) Harding, V. J.: *Physiol. Rev.* 5: 279, 1925. (35) Bauer, W., Aub, J. C., and Albright, F.: *J. Exper. Med.* 49: 145, 1929. (36) *Idem*: *J. Clin. Investigation* 7: 75, 1929.

EFFECT OF VITAMIN K ADMINISTERED TO PATIENTS IN LABOR*

J. E. FITZGERALD, M.D., AND AUGUSTA WEBSTER, M.D., CHICAGO, ILL.

SINCE its discovery by Dam,¹⁻⁵ vitamin K has been used successfully in the treatment of hemorrhagic disease of the newborn,²²⁻²⁴ and in the management of obstructive jaundice, before and after operation.^{14-18, 21}

A number of investigations have been made on the prothrombin content of human blood, especially that of the newborn.³¹⁻³⁵ The results of these determinations have been somewhat confusing because of the various methods used to determine the prothrombin level.²⁴ In the two-stage method,^{27, 29, 30} prothrombin is changed to thrombin in a preliminary step, and the thrombin formed is then titrated by means of a dilution technique. This method is excellent for research purposes but is too complicated for routine clinical use. In the Quick^{22, 28} method thromboplastin is added to blood plasma, and the supposition is that thrombin is rapidly built up to the clotting level, and clotting therefore occurs before all of the prothrombin has been converted. The rate at which prothrombin can be built up to the clotting level depends both on the amount of prothrombin present and upon its "convertibility." This method, therefore, measures both the amount of prothrombin, and the convertibility of the prothrombin, and is a summation of these two factors. It does not show simply the amount of prothrombin present. It is the opinion of Owen, Hoffman, Ziffren and Smith²⁴ that conversion occurs quite rapidly in the plasma of newborn infants, and that this fact compensates for a relative deficiency in amount.

The "bedside" test of Smith and others²⁶ is similar in principle to the Quick method, except that the thromboplastin is added directly to whole blood instead of to plasma; it does not require centrifuging of the blood, and can be done as its name suggests at the bedside. Like the Quick test the amount of prothrombin present and the ease of its con-

*Presented at a meeting of the Chicago Gynecological Society, April 19, 1940.

In our study the Abbott preparation of Klotogen was used. This is put up in gelatin capsules, each of which contains 1,000 Almquist units. Each of these units is equivalent to approximately 37.5 Dam units. Four capsules were given in one dose during labor to each patient and 10 gr. of bile salts were given at the same time. Blood was drawn from the cubital vein of the mother before the K was given. At the time of delivery, blood was again taken from the mother and also from the umbilical cord of the infant. The percentage prothrombin was determined on each sample at the time it was obtained by the method described above. All of the tests were made by the same individual, who is a registered technician, and the same procedure was carried out in each case.

OBSERVATIONS

The patients used in this study were normal in all respects. They were at full term and free from venereal disease. They were all afebrile. In every case the blood pressure was within normal limits. There were no cases of prolonged labor and every patient delivered spontaneously, and no analgesic was used except where noted.

Table I shows the results in 25 untreated patients. Prothrombin levels were determined on the mother before and after delivery, and on the baby at birth. Determinations on the babies were made on cord blood. Investigation of the chart shows little difference in maternal prothrombin before and after delivery. Eight cases showed the prothrombin level slightly lower after labor; 14 showed slightly higher post-partum levels; 3 cases were the same before and after labor. The average maternal prothrombin before delivery was 95.2 per cent of normal; after labor it was 97.1 per cent. Such results suggest that normal labor has no effect on the maternal prothrombin, and that the method used for these determinations has a high degree of accuracy. The babies ranged in weight from 5 pounds 13 ounces

TABLE I. CONTROL GROUP

AGE	RACE	BLOOD PRESSURE	GRAV.	PROTHROMBIN		% CORD BLOOD	WT. OF BABY
				% ON ENTRANCE	% AT DELIVERY		
19	C	126/86	i	84	87	140	6 lb.
25	W	108/74	ii	85	85	125	6 lb. 7 oz.
21	C	120/84	i	87	83	118	6 lb. 5 oz.
21	W	110/60	i	88	83	120	6 lb. 5 oz.
19	W	119/76	i	92	86	130	8 lb. 9 oz.
16	C	120/70	i	92	92	96	6 lb. 1 oz.
22	W	110/65	i	93	90	190	6 lb. 6 oz.
25	C	90/70	v	93	95	139	8 lb. 7 oz.
22	C	136/96	i	95	92	122	7 lb. 5 oz.
29	C	120/90	i	95	96	144	6 lb. 4 oz.
30	W	132/60	ii	95	97	144	7 lb. 7 oz.
26	W	130/88	iii	95	97	119	6 lb. 5 oz.
22	C	98/50	iv	95	100	139	8 lb. 7 oz.
27	W	120/70	ii	95	103	130	7 lb. 5 oz.
24	C	112/74	i	97	96	105	7 lb. 2 oz.
31	C	118/65	i	97	99	134	7 lb. 9.5 oz.
15	C	120/80	i	98	100	144	5 lb. 13 oz.
18	W	120/68	i	98	107	139	6 lb. 8 oz.
23	C	132/80	iv	100	100	153	6 lb. 12 oz.
22	C	122/80	ii	100	105	123	7 lb. 12 oz.
23	C	132/80	iv	100	105	153	6 lb. 12 oz.
27	C	130/100	viii	100	107	139	8 lb. 7 oz.
17	C	126/80	i	104	108	162	6 lb. 8 oz.
23	W	110/65	iii	108	106	123	8 lb. 1 oz.
15	W	148/90	i	114	110	190	6 lb. 6 oz.
Average				96.1	97.1	135.2	

In the current March 2 issue of the *Journal of the American Medical Association*, Kato and Poncher³⁶ report a microprothrombin test which requires only a drop (from 10 to 15 c. mm.) of blood and which therefore should prove very useful in work with newborn infants. This test measures the clotting time according to this particular system rather than the actual amount of prothrombin present. They had a large series of 173 newborn infants, on which they made 1,595 tests. They found the prothrombin clotting time to be prolonged on the first day of life,

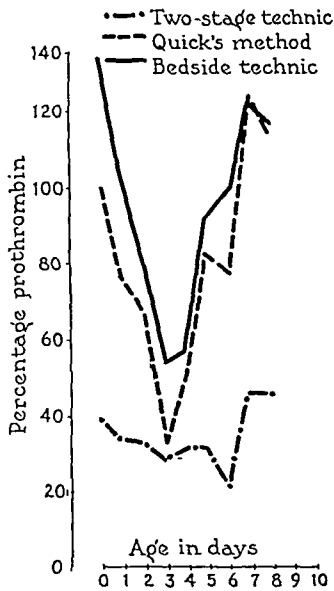


Fig. 1.—Average prothrombin levels in newborn by different techniques, from the figures of Owen, Hoffman, Ziffren and Smith.²⁴

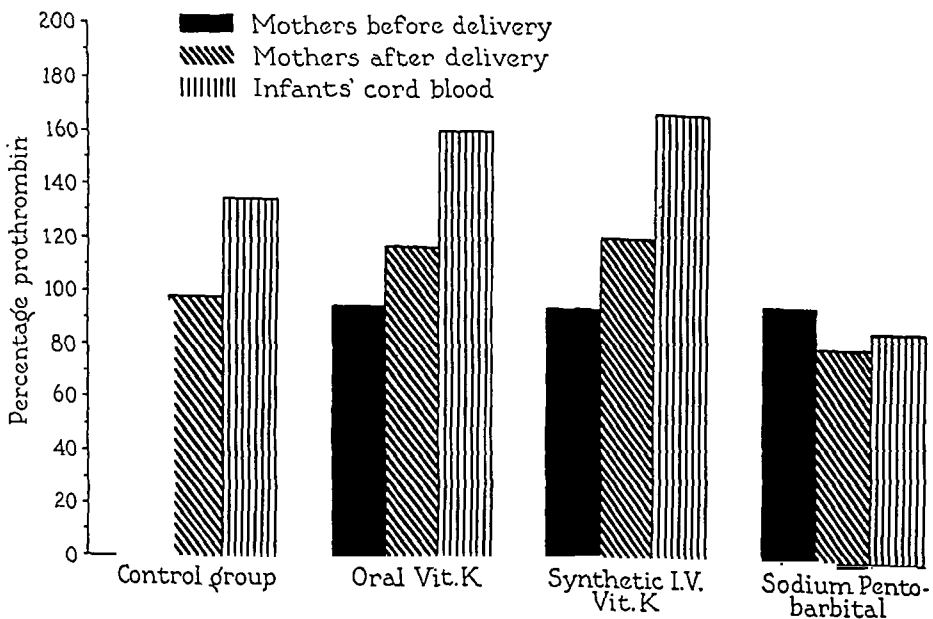


Fig. 2.—Graph showing average prothrombin readings in each group studied.

averaging 43.2 seconds for mature babies, and 46.5 seconds for immature babies, and that it gradually decreased so that the average on the tenth day was 25 seconds. The normal adult capillary whole blood clots in twenty seconds by this method. Their findings in the mature and immature infants were essentially the same.

upon the amount of prothrombin present and an X factor which governs the rate at which the prothrombin can be converted into thrombin. Thus it may be shown by a two-stage technique that the chemical level of prothrombin in the newborn is definitely lower than in a normal adult. Nevertheless our results show that routinely the cord blood of a full-term newborn infant clots faster than does that of the normal adult.

Table II shows the results of 50 cases in which the mother was given 4,000 Almquist units of vitamin K with 10 gr. of bile salts orally during labor. This medication was given from forty-five minutes to twenty-six hours before delivery. Forty-eight, or 96 per cent, of the mothers showed a higher prothrombin level at delivery than they showed before the administration of vitamin K. There is, of course, considerable variation in the prothrombin level of untreated cases, but regardless of the initial level the post-partum level was higher, except for the two cases noted. The average increase in prothrombin level was 21.3 points. The newborn showed a corresponding rise. The newborn of the untreated mothers all showed a higher level than that of the mothers. Of the newborn of the treated mothers, 94 per cent showed a prothrombin level higher than that of the mother at delivery, and 6 per cent showed the same level. This is significant because 96 per cent of the treated mothers showed a definite increase in prothrombin level, apparently due to treatment. The prothrombin level of the newborn of treated mothers was 160.2 per cent, compared to 135.2 per cent in the newborn of untreated mothers. Thus it seems clear that by the oral administration of Klotogen plus bile salts to a mother during labor there will result an elevation of the prothrombin level of both mother and child.

If the vitamin K be given intravenously in approximately the same doses (synthetic K - 2 methyl- 1:4 naphthoquinone), the results are similar. One dose of 2 mg. was given each of 19 patients (Table III). The time of administration was from fifty minutes to twenty-three hours and fifteen minutes before delivery. With one exception every mother showed a higher prothrombin level at delivery than before medication, and this one case was practically unchanged. Every cord blood showed a higher level than did the mother at delivery. The average gain for the mother was 26 points, and the babies averaged 30 points more than the babies of untreated mothers.

TABLE III. SYNTHETIC VITAMIN K

AGE	RACE	BLOOD PRESSURE	GRAV.	PROTHROMBIN		TIME ELAPSED	CORD %	WT. OF BABY
				% ON EN-TRANSE	% ON DE-LIVERY			
19	C	136/86	i	71	92	3 hr. 50 m.	109	6 lb. 3 oz.
21	C	126/86	i	81	90	1 hr. 35 m.	135	7 lb. 4 oz.
22	W	-----	iii	90	123	5 hr. 30 m.	142	7 lb. 3 oz.
24	C	130/88	iii	91	110	4 hr. 40 m.	216	7 lb. 1 oz.
16	C	104/60	i	92	103	2 hr. 20 m.	138	6 lb. 10 oz.
19	C	130/88	i	92	119	4 hr. 10 m.	165	7 lb. 10 oz.
17	C	116/70	i	93	110	1 hr. 55 m.	155	6 lb. 10 oz.
24	C	142/70	i	95	151	1 hr. 45 m.	180	7 lb.
32	W	122/80	i	96	115	2 hr. 20 m.	200	7 lb. 11 oz.
20	C	130/64	vi	97	110	1 hr. 35 m.	160	6 lb. 1 oz.
25	W	130/90	i	98	112	22 hr. 35 m.	118	9 lb. 3 oz.
28	W	118/70	iii	100	106	1 hr. 15 m.	165	7 lb. 8 oz.
23	W	-----	i	100	113	2 hr. 45 m.	245	8 lb. 4 oz.
28	C	130/90	vii	100	122	50 m.	173	7 lb. 9 oz.
22	C	122/74	iii	100	133	55 m.	183	6 lb. 6 oz.
26	W	112/68	ii	100	165	23 hr. 15 m.	200	6 lb.
30	W	130/80	iv	100	169	2 hr. 35 m.	186	5 lb.
27	C	130/72	iii	103	100	3 hr. 25 m.	189	7 lb. 15 oz.
28	C	138/86	iv	110	138	2 hr. 15 m.	138	7 lb. 4 oz.
Average				94.2	120.3		166.7	

to 8 pounds 9 ounces. Prothrombin levels averaged 136.8 per cent of normal adult readings, and in every instance the prothrombin level in the babies' blood was higher than that of the maternal blood.

It should be remembered that throughout this discussion *prothrombin level* does not refer to the actual amount of prothrombin present in the blood, but rather to the *ability of the blood to clot*, which depends

TABLE II. GROUP RECEIVED ORALLY 4,000 ALMQUIST UNITS OF VITAMIN K AND 10 GR. OF BILE SALTS

AGE	RACE	BLOOD PRESSURE	GRAV.	BEFORE K %	TIME ELAPSED	AFTER K %	CORD %	WT. OF BABY
22	W	126/78	i	40	1 hr. 35 m.	59	104	6 lb. 9 oz.
18	C	124/82	i	57	1 hr.	66	109	8 lb. 1½ oz.
23	C	119/78	iii	69	1 hr. 55 m.	88	88	7 lb. 2 oz.
25	W	108/90	iii	70	6 hr.	97	143	7 lb. 10 oz.
27	C	127/82	i	73	3 hr. 55 m.	85	91	7 lb. 7 oz.
41	W	110/70	ix	78	3 hr.	114	192	6 lb. 14 oz.
15	C	102/88	i	81	2 hr. 25 m.	90	208	7 lb. 1 oz.
18	C	114/86	ii	82	9 hr.	92	115	6 lb. 11 oz.
22	W	128/74	i	83	9 hr. 40 m.	88	140	4 lb. 7 oz.
21	W	125/79	i	83	3½ hr.	192	158	5 lb. 14 oz.
36	W	135/86	v	85	3 hr.	96	114	6 lb. 10 oz.
25	W	108/80	ii	86	45 m.	109	141	6 lb. 10 oz.
19	W	104/54	i	88	2 hr. 40 m.	117	128	5 lb. 7 oz.
38	C	126/88	iv	90	3 hr. 35 m.	100	114	6 lb. 15 oz.
22	W	127/82	i	90	2 hr. 35 m.	148	220	8 lb. 2 oz.
19	C	114/78	ii	91	2 hr.	100	182	6 lb. 10 oz.
21	C	128/60	i	92	4 hr. 25 m.	115	170	7 lb. 2 oz.
21	C	134/74	i	93	26 hr.	114	240	8 lb. 12 oz.
23	W	110/80	ii	94	24 hr.	105	170	9 lb. 4 oz.
17	C	118/70	i	94	2 hr. 15 m.	124	167	6 lb. 9 oz.
22	W	140/98	i	94	5 hr.	120	247	6 lb. 6 oz.
22	W	132/88	i	95	4½ hr.	114	170	6 lb. 8 oz.
19	C	140/90	ii	95	4 hr. 20 m.	117	265	6 lb. 2 oz.
34	W	120/82	iv	95	5 hr.	119	145	9 lb.
19	W	120/70	i	95	9 hr.	130	130	4 lb. 6 oz.
21	C	136/80	i	95	1 hr. 45 m.	156	147	7 lb. 7½ oz.
22	W	120/80	iii	96	2 hr.	115	177	6 lb. 5 oz.
17	W	110/80	i	96	3 hr.	114	192	7 lb.
28	W	124/80	iii	96	4 hr.	120	141	7 lb.
32	W	120/80	i	100	3 hr.	105	105	6 lb. 10 oz.
24	C	128/82	ii	100	1 hr. 25 m.	107	160	7 lb. 2 oz.
18	W	134/90	i	100	1 hr. 30 m.	112	150	8 lb. 1 oz.
21	C	132/80	i	100	2½ hr.	120	148	6 lb. 7 oz.
25	W	138/80	iv	100	5 hr.	129	175	7 lb. 8 oz.
16	C	124/78	i	100	3 hr. 15 m.	170	170	7 lb. 5 oz.
17	W	104/60	i	103	4 hr. 20 m.	95	205	7 lb. 2 oz.
32	W	132/90	iv	104	5 hr.	109	135	7 lb. 8 oz.
24	C	98/68	iii	104	20 hr.	112	160	8 lb. 1 oz.
19	C	130/90	ii	104	4 hr.	121	153	8 lb. 2 oz.
25	C	130/78	iv	105	1 hr. 35 m.	112	136	7 lb. 6 oz.
16	C	136/88	i	105	3 hr.	124	181	5 lb. 13½ oz.
25	W	132/80	ii	105	3 hr. 35 m.	129	200	8 lb. 1 oz.
16	C	102/82	ii	106	3½ hr.	135	135	7 lb. 8 oz.
16	C	114/80	ii	108	10 hr. 55 m.	168	186	8 lb. 3 oz.
30	W	136/90	iv	109	1 hr. 10 m.	128	144	9 lb.
19	C	128/82	ii	110	6 hr. 35 m.	97	123	8 lb. 2 oz.
24	C	138/78	iii	111	1 hr. 15 m.	148	170	6 lb. 1 oz.
23	C	120/92	ii	113	2 hr.	131	160	8 lb. 14 oz.
22	C	120/70	ii	113	1 hr. 45 m.	133	200	7 lb. 5 oz.
20	C	138/96	ii	143	2½ hr.	190	266	7 lb. 5 oz.
Average				95.5		116.8	160.2	

In an effort to determine whether or not we could prevent this change, we gave vitamin K (Table V) to a few patients who had the same drug for analgesia. The series is wholly inadequate for this purpose, because it is so small, but suggests the value of continued investigation along this line.

SUMMARY

1. A series of cases has been studied in an effort to determine the effect of vitamin K administered to women in labor.

2. Control cases show practically no change in the maternal prothrombin during and after labor.

3. Patients treated with oral klotogen during labor show a definite rise in the maternal prothrombin level at the end of labor. There is also a definite rise in the average level of the cord blood.

4. Patients treated with intravenous synthetic vitamin K show approximately the same elevation of prothrombin levels.

5. A small series of cases that was given sodium pentobarbital as an analgesic showed a definite depression in the prothrombin level of both mother and child.

6. This depression probably can be prevented by the proper use of vitamin K.

7. This paper should be considered as a preliminary report of work still in progress.

REFERENCES

- (1) *Dam, H.*: Biochem. Ztschr. 215: 475, 1929. (2) *Idem*: Ibid. 220: 158, 1930.
- (3) *Dam, Henrik, and Schonheyder, Fritz*: Biochem. J. 28: 1355, 1934. (4) *Dam, H.*: Biochem. J. 29: 1273, 1935. (5) *Dam, H., Schonheyder, F., and Tage-Hansen, E.*: Biochem. J. 30: 1075, 1936. (6) *Almquist, H. J., and Stockstad, E. L. R.*: Nature 136: 31, 1935. (7) *Idem*: J. Nutrition 12: 329, 1936. (8) *Clark, R. L. Jr., Dixon, C. F., Butt, H. R., and Snell, A. M.*: Proc. Staff Meet. Mayo Clinic 14: 407, 1939. (9) *Smith, H. P., Warner, E. D., and Brinkhous, K. M.*: J. Exper. Med. 66: 801, 1937. (10) *Greaves, J. D., and Schmidt, C. L. A.*: Proc. Soc. Exper. Biol. & Med. 37: 43, 1937. (11) *Hawkins, W. B., and Brinkhous, K. M.*: J. Exper. Med. 63: 795, 1936. (12) *Quick, A. J.*: Am. J. Physiol. 118: 260, 1937. (13) *Quick, A. J., Stanley-Brown, Margaret, and Bancroft, F. W.*: Am. J. M. Sc. 190: 501, 1935. (14) *Warner, E. D., Brinkhous, K. M., and Smith, H. P.*: Proc. Soc. Exper. Biol. & Med. 37: 628, 1938. (15) *Butt, H. R., Snell, A. M., and Osterberg, A. E.*: Proc. Staff Meet., Mayo Clinic 13: 74, 1938. (16) *Snell, A. M., Butt, H. R., and Osterberg, A. E.*: Am. J. Digest Dis. & Nutrition 5: 590, 1938. (17) *Butt, H. R., Snell, A. M., and Osterberg, A. E.*: Proc. Staff Meet. Mayo Clinic. 13: 753, 1938. (18) *Stewart, J. D., and Rourke, G. M.*: J. A. M. A. 113: 2223, 1939. (19) *Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R.*: J. A. M. A. 113: 380, 1939. (20) *Scanlon, Geo. H., Brinkhous, K. M., Warner, E. D., Smith, H. P., and Flynn, J. E.*: J. A. M. A. 112: 1898, 1939. (21) *Butt, H. R., Snell, A. M., and Osterberg, A. E.*: J. A. M. A. 113: 383, 1939. (22) *Quick, A. J., and Grossman, A. M.*: Am. J. M. Sc. 199: 1, 1940. (23) *Waddell, W. W., Jr., and Guerry, DuPont, III*: J. A. M. A. 112: 2259, 1939. (24) *Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P.*: Proc. Soc. Exper. Biol. & Med. 41: 181, 1939. (25) *Quick, A. J.*: Am. J. Physiol. 114: 282, 1936. (26) *Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R.*: J. A. M. A. 113: 380, 1939. (27) *Warner, E. D., Brinkhous, K. M., and Smith, H. P.*: Am. J. Physiol. 114: 667, 1936. (28) *Quick, A. J.*: J. A. M. A. 110: 1658, 1938. (29) *Brinkhous, K. M., Smith, H. P., and Warner, E. D.*: Am. J. M. Sc. 193: 475, 1937. (30) *Warner, E. D., Brinkhous, K. M., and Smith, H. P.*: Am. J. Physiol. 114: 667, 1936. (31) *Quick, A. J., and Grossman, A. M.*: Proc. Soc. Exper. Biol. & Med. 40: 647, 1939. (32) *Idem*: Am. J. M. Sc. 199: 1, 1940. (33) *Dam, H., Tage-Hansen, E., and Plum, P.*: Lancet 2: 1157, 1939. (34) *Hellman, L. M., and Shettles,*

TABLE IV. SODIUM PENTOBARBITAL GR. 7½

AGE	RACE	BLOOD PRESSURE	GRAV.	% PROTH. ON ENT.	TIME ELAP.	AT DEL. %	CORD %	WT. OF BABY
22	W	118/74	i	57	7 hr.	50	53	8 lb. 12 oz.
22	W	130/88	i	83	2 hr.	79	90	6 lb. 7 oz.
17	C	124/86	i	87	4 hr. 25 m.	68	100	8 lb.
22	W	130/90	i	92	9 hr. 35 m.	92	104	7 lb. 12 oz.
21	C	110/74	i	93	2 hr. 50 m.	84	140	6 lb. 7 oz.
22	C	130/80	i	96	5 hr. 25 m.	90	100	7 lb. 11 oz.
25	W	132/90	i	96	9 hr. 5 m.	90	104	6 lb. 9 oz.
19	C	138/88	i	97	8 hr.	90	60	7 lb. 2 oz.
18	C	120/80	i	98	3 hr. 30 m.	90	100	6 lb. 2 oz.
23	W	120/80	i	100	3 hr. 30 m.	74	92	6 lb. 2 oz.
18	C	114/62	i	100	3 hr. 50 m.	84	95	7 lb.
21	C	134/90	i	100	5 hr. 30 m.	89	121	7 lb. 10 oz.
27	C	138/84	ii	100	2 hr. 30 m.	90	104	6 lb. 9 oz.
23	W	122/94	i	100	1 hr. 10 m.	94	61	6 lb. 7 oz.
20	W	138/82	i	100	4 hr. 45 m.	103	60	6 lb.
19	C	128/62	ii	102	2 hr. 10 m.	90	60	6 lb. 2 oz.
20	W	130/88	i	103	2 hr.	106	63	7 lb. 3 oz.
28	W	110/80	i	104	9 hr.	80	73	8 lb.
31	W	120/78	iii	110	4 hr.	79	57	6 lb. 1 oz.
17	C	127/76	i	112	9 hr.	76	70	6 lb. 4 oz.
Average				96.5		80.4	85.3	

The cases considered so far have had no medication except the vitamin K. Table IV shows the results of a small series in which sodium pentobarbital was used as an analgesic. Of these 13 mothers only two had as high a prothrombin level at delivery as they did on entrance. The average loss was 14 points. This is in marked contrast to the untreated control group in which there was practically no variation in the prothrombin level before and after delivery. The findings in the newborn are still more striking. In less than half of the cases was the prothrombin level of the newborn as high as that of the mother at delivery and in 10 out of 13 the newborn prothrombin level was lower than that of the mother on entrance. The average prothrombin level of the newborn was 75.5 per cent, compared to an average level of 135.2 per cent in the untreated cases, and 160.2 per cent and 166.7 per cent of the treated cases. We are unable to explain this lower prothrombin level in the cases which had sodium pentobarbital as an analgesic. The method which we used for the determination of the prothrombin level measures the clotting ability of the blood, which depends upon the amount of prothrombin present and the rate at which it can be converted into thrombin. It seems reasonable to suppose that the actual amount of prothrombin in the mother and the newborn can hardly be diminished in so short a time, and that what happens is a disturbance of the rate at which the prothrombin can be converted.

TABLE V. NEMBUTAL GR. 7½ WITH VITAMIN K

AGE	RACE	BLOOD PRESSURE	GRAV.	BEFORE K AND NEMBUTAL %	TIME ELAP.	AFTER K %	CORD %	WT. OF BABY
21	W	128/82	i	96	32 hr.	51	78	7 lb. 4 oz.
22	W	148/84	i	76	8 hr.	74	44	7 lb. 1 oz.
20	C	98/56	i	143	2½ hr.	135	153	8 lb. 1 oz.
19	W	118/88	i	96	12 hr.	112	124	6 lb. 5½ oz.
20	W	128/84	i	104	3 hr. 30 m.	157	137	7 lb. 7 oz.
24	W	124/90	v	110	2 hr. 10 m.	105	105	9 lb.
18	C	146/70	i	84	1 hr. 35 m.	79	130	7 lb. 6 oz.
Average				709		713	771	
				101.3		101.8	110.1	

definite depressant effect on the glycogenolytic power of the liver. The mechanism of this effect is entirely speculative and will require further investigation. I feel there is definite promise in this type of study, not only from the point of view of the effect of barbiturates on the maternal body mechanism but also on that of the baby both before and after delivery. This is a study in itself and time will not permit a discussion of it at this time.

DR. W. J. DIECKMANN.—Attention must be called to the excellent work done by the biochemists. Vitamin K has only been known for several years and yet chemists have isolated and synthesized it.

Dr. Fitzgerald's data are interesting and his figures are all very exact. The prothrombin time and clotting time may vary. All reports to date indicate that vitamin K is of no value during the labor of normal patients to shorten the clotting time of the blood in the hope of preventing post-partum hemorrhage. Sufficient evidence has accumulated to show that the baby on the fifth or sixth day does have a decrease in its prothrombin time. If the baby shows any evidence of bleeding, vitamin K should be given. If the prothrombin time is prolonged and if facilities are not available for its determination, vitamin K should be given empirically. It is especially the premature baby that is likely to have a prolonged prothrombin time, and it may be found advisable to routinely administer vitamin K to these babies or to the mothers during labor. It may also be found advisable to administer vitamin K to the mother or to the baby where labor is long or the delivery difficult.

DR. FITZGERALD (closing).—I wonder if the cases in which Dr. Olwin found a variable prothrombin time before and after labor, had had some ethylene, and whether that might also be a factor.

As to Dr. Dieckmann's question, we made no investigation of the effect on babies of mothers who had either a long or a particularly difficult labor. This work is in progress now. We have presented a rather small series which may seem to show some very definite evidence that there may be an alteration in the prothrombin level of the mother and baby if treated during labor, and also that there is some good evidence that sedatives may lower this level. We were interested in finding out whether we could keep this level up by administering vitamin K. We are studying a series to find out what happens to the prothrombin level of the mother and baby in long labors, also in the premature baby and the effect of giving vitamin K to mothers in an effort to keep the fetal prothrombin level up to normal.

MORAL ASPECTS OF THERAPEUTIC ABORTION*

THOMAS V. MOORE, M.D., WASHINGTON, D. C.

WHEN the question is raised whether or not it is right to induce abortion, it implies that one may draw a conclusion one way or another in determining a stand on this important problem. Whenever a conclusion is drawn, there must be in the mind of the reasoner a general principle which determines what conclusion is to be deduced.

For many years physicians have considered themselves justified in performing an abortion when they considered that the physical well-being of the mother would be in serious jeopardy if a pregnancy were allowed to come to term. What principle governed the conclusion to which this general attitude may be ascribed?

The principle has thus been expressed by Hirst, in his textbook on obstetrics.

*Paper read at a symposium on Abortion at the Johns Hopkins Medical School, March 1, 1940.

L. B.: Johns Hopkins Hosp. Bull. 65: 138, 1939. (35) *Shettles, L. B., Delfs, E., and Hellman, L. M.*: Johns Hopkins Hosp. Bull. 65: 419, 1939. (36) *Kato, K., and Poncher, H. G.*: J. A. M. A. 114: 749, 1940.

104 S. MICHIGAN AVENUE
30 N. MICHIGAN AVENUE

DISCUSSION

DR. JOHN H. OLWIN.—As Dr. Fitzgerald has told you, there are at present three methods of measuring the prothrombin clotting activity of the blood, the Quick method, the bedside technique of the group at Iowa, where I feel the best work in this field is being done, and the two-stage method. As he mentioned, the one-stage method, either the Quick method or the bedside technique, measures not only the amount of prothrombin but the conversion activity of the prothrombin, and in addition the anticoagulant factors come into play. Fibrinogen and calcium vary little in the blood in most patients even in disease and this variation apparently has little effect on the clotting activity of the blood. The thromboplastic factor is highly variable and as yet we have no satisfactory method for measuring it, though Dr. Smith and his associates have laid the groundwork for such a test. In the two-stage method the plasma is first freed of fibrinogen, the prothrombin is converted to thrombin, and in a separate stage the thrombin is allowed to act on prepared beef fibrinogen. The number of units of prothrombin are estimated and compared to the number in normal control plasmas, thus giving the percentage of prothrombin in the plasma in question.

During the last seven or eight months in connection with our obstetric department, we have been studying prothrombin levels of normal pregnancy. These vary a great deal. Some of the women have as high as 150 per cent prothrombin levels during normal pregnancy. Some maintain these high levels practically throughout the course of pregnancy up to the time of delivery. Others drop to near normal or below. If they are running in the high brackets, they usually stay there. Some may vary as much as 50 points, however. Just why this great variation we do not know. Some we have studied began to taper off about term. Shortly after delivery, twenty-four to forty-eight hours, they begin to climb again. This may be on the basis of the concentration of the blood at this time. These determinations have been made by the two-stage method. Our studies are as yet very incomplete.

The two methods under discussion, the "bedside method" and the two-stage technique, roughly follow each other in the measure of prothrombin. Individual tests, however, may vary as much as 50 per cent. The percentage of error in the two-stage method is about 3 per cent. It should be borne in mind that one is measuring several factors, the other, so far as we can determine, only one factor.

During the last week we have studied 3 cases in which we have administered nembutal before delivery. These are certainly too few cases to draw conclusions on. (I have slides illustrating this study.) Two cases showed no appreciable change in prothrombin level following the administration of 6 gr. of nembutal. One case showed a drop of 18.5 per cent. Control cases receiving only ethylene showed a similar drop or no change at all. Our results, as you see, do not quite correspond to the results we have seen in the paper presented by Dr. Fitzgerald. In spite of that I feel the point of this paper is well taken.

There is good evidence to indicate that prothrombin is made in the liver. Hepa-tomized dogs show an immediate marked drop in prothrombin. Dogs under chloroform anesthesia show a rapid fall in prothrombin and the return to normal level is commensurate with the time required for complete liver regeneration. Patients with toxic hepatitis, cirrhosis and acute yellow atrophy have a lowered blood prothrombin and respond poorly or not at all to vitamin K therapy.

Hrubetz and Blackberg in the last few years have studied several series of rabbits to which they administered nembutal, phenobarbital, and other barbiturates intraperitoneally, in order to study the effect of the drugs on the ability of the liver to mobilize glycogen. Normal rabbits show a marked increase in blood sugar after the injection of epinephrine. So far as we know the higher barbiturates, as nembutal, pentothal, etc., are detoxified in the liver. Phenobarbital on the other hand is eliminated by the kidneys. All of the barbiturates studied showed a

If this is the case, one may well ask what right has the physician to perform the second stage of craniotomy "to avoid the painful experience of seeing the child gasp after delivery"?

If the second stage of the operation is omitted and the physician attempts to effect delivery with as little loss of cerebral substance as possible and does all he can to save the life of the child, he is no longer making a direct attempt to kill the child but in certain rare instances in which delivery may be otherwise impossible, he will be doing all he possibly can do to save the lives, both of the child and of the mother.

Can he apply Hirst's principle to any such emergencies and say that he is attempting to save one life and that, the more valuable of the two, instead of sacrificing both mother and fetus, if he perforates the infant's skull and then makes a direct attempt to kill the child by a complete destruction of the cranial contents? The principle which seems so plausible simply does not apply, and the physician kills a child who might otherwise have lived and perhaps have become a normal human being.

The second problem is the termination of ectopic gestation. Until recently, the attitude of Catholic theologians has been that cases of ectopic gestation must be allowed to progress until an actual hemorrhage justifies intervention, lest the mother bleed to death. The principle has been maintained that the physician cannot lawfully kill the child by expulsion when it is not viable, even in order to save the mother's life. It has been the constant opinion of Catholic theologians that the extraction of a living nonviable child is a direct attack on its life and, therefore, contrary to sound morality.

Some years ago Vermeersch, a famous Jesuit, Professor of Moral Theology at the Gregorian University in Rome, had one of his students⁵ study the problem in the light of pathology, and the following attitude was developed.

In normal pregnancy the placental villi grow into the thick uterine mucosa, breaking into capillary blood vessels, and so in the tiny surrounding spaces they are bathed with maternal blood and the fetus absorbs oxygen and nourishment from the mother. But when pregnancy occurs in the Fallopian tube, the thin mucosa is no longer an adequate barrier and the villi erode large blood vessels, so that the mother bleeds more or less severely into the tissues of the tube. A fatal termination is possible unless this bleeding is stopped. But it is always lawful to stop bleeding in order to save the patient's life, even if in so doing the death of a fetus would result. Thus one might imagine stab wounds producing hemorrhages which, if not controlled, would lead to the death of a pregnant woman, but of such a character that if the arteries are tied, the blood supply to the fetus is cut off and the fetus will die. Every Catholic theologian would recognize the right and the duty of the physician to control the hemorrhage in such a situation, even if in so doing the death of the fetus would be a concomitant result.

This is an example of the principle of double effect, perfectly logical and justifiable in itself, though at times difficult of application. It may thus be stated: Whenever two effects flow from one and the same act,

The induction of abortion should be undertaken as reluctantly as one would commit justifiable homicide. If in the course of pregnancy some disease arises as a direct consequence of gestation, or if a woman suffering from disease is made much worse by the existence of pregnancy, and if her life is distinctly endangered in consequence, it is not only justifiable, but it is the physician's duty to terminate gestation, and thus to save one life, and that the more valuable of the two, instead of sacrificing both mother and fetus.¹

We might crystallize the general principle embodied in this statement somewhat as follows:

Whenever the physician knows that the mother will die or her mental or physical health be seriously impaired if a pregnancy is allowed to go on to term and that he can save her life or her health by inducing an abortion, he has a right to kill the child in order that the mother may live and maintain her normal health.

There are three classes of cases to which the principle has been applied.

- a. Those in which craniotomy has seemed to be the only possibility of saving the mother's life.
- b. Cases of ectopic gestation.
- c. Those in which pregnancy has been thought to be dangerous for the mother, should it be allowed to go on to term.

It is the latter problem with which this symposium is primarily concerned, but for the sake of rounding out the discussion I would first like to dwell briefly on the operation of craniotomy and the problem of ectopic gestation.

The operation of craniotomy involves two stages:

- a. Perforation of the skull.
- b. Complete destruction of the cerebral contents. In the words of De Lee, "the brain matter is thoroughly broken by means of a long forceps, taking special care to tear the tentorium and destroy the medulla, this to avoid the painful experience of seeing the child gasp after delivery."²

As I have pointed out in my *Principles of Ethics*,³ the second stage of the operation became a general recommendation by reason of the fact that physicians from time to time were horrified by the delivery of a living child, in spite of the fact that much of its cerebral tissue had been destroyed.

From the fact now abundantly demonstrated that adults may survive very extensive removals of cerebral tissue and preserve mentality practically intact, one might well raise the question whether or not the child with its plastic nervous system might survive the loss of a considerable amount of cerebral tissue and still be able to develop a normal mental life.

If one looks into the literature, one will find cases of survival after craniotomy in spite of the fact that no steps were taken to control hemorrhage or limit the loss of cerebral tissue to the minimum required to reduce the cranial circumference so that delivery would be possible. The cases are few, but it would seem that a child may later manifest normal mentality in spite of delivery by craniotomy and may even live on into adult years.⁴

It would seem, therefore, that one of the fundamental statements involved in the principle justifying therapeutic abortion cannot be made. No physician can say with certainty: If this pregnancy is not terminated promptly, the mother will die or her health be seriously impaired. On the other hand, he cannot say with certainty: If this pregnancy is terminated promptly by abortion, the mother will live.

Let us now look again at the principle by which therapeutic abortion is justified.

Whenever the physician knows that the mother will die if a pregnancy is allowed to go on to term and that he can save her life by inducing an abortion, he has a right to kill the child that the mother may live.

It would appear that one must introduce instead of "knows" some such phrase as "thinks it more likely" that the mother will die if pregnancy goes on to term, and that she may not die if she submits to an abortion.

What chance has the mother of living if she submits to an abortion? So much here depends on her own physical condition that statistics on mortality in general for abortions performed on healthy women by skilled physicians would give no pertinent information governing any individual case. Various German clinics report a mortality rate of 1.9 to 5.4 per cent.¹¹ The Russian operators who perform 25 to 30 abortions a day and are operating on healthy young women have a mortality rate of about one one-hundredth of 1 per cent.¹²

But when one performs a therapeutic abortion, he operates on a woman who is already seriously ill, and a great deal depends on her actual condition.

When, therefore, the problem of the physician's knowledge in relation to the outcome is looked at squarely, one must admit that:

- a. The mother may die.
- b. The fundamental disease, which was considered an indication for abortion, may be aggravated.¹³
- c. Various remote results of an undesirable character may follow.

Thus Taussig reports on the Russian experiment: "Even the most enthusiastic of the Russian advocates of legalized abortion are, however, appalled at the growing evidence of serious pelvic disturbances, endocrine dysfunctions, sterility, ectopic pregnancy, and other complications following in the wake of artificial abortions."¹⁴

When confronted, therefore, with the problem of undertaking a therapeutic abortion, the physician of our day can no longer ease his conscience by taking refuge behind Hirst's principle: "It is not only justifiable, but it is the physician's duty to terminate gestation and thus to save one life and that the more valuable of the two, instead of sacrificing both the mother and the fetus."

He must envisage the following possibilities, and perhaps make to the family of the patient some such representations as these:

- a. If the patient submits to an abortion, she may die from its effects, but in my own opinion she is more likely to live.
- b. If she survives the abortion, the disease from which she is suffering may be aggravated, but I trust this will not be the case.
- c. If she recovers, there may be various remote complications, such as pelvic disorders, dysmenorrhea, sterility, etc., and future pregnancies may be complicated and dangerous.

one good and the other bad, and the agent honestly intends the good effect, the act may be considered justifiable and the bad effect be looked upon as not aimed at or desired for its own sake.

When, therefore, a physician ties or clamps the Fallopian tubes on either side of an ectopic fetus and intends thereby to stop a hemorrhagic process which endangers the mother's life, his act is honestly an attempt to stop bleeding and not an attempt to kill a child.

Let us now turn to the problems of therapeutic abortion. If we look at Hirst's principle as applied to therapeutic abortion, it involves the three following statements.

I. If this pregnancy is not terminated promptly, the mother will die or her mental or physical health will be seriously impaired.

II. If this pregnancy is terminated promptly, the mother will live and her mental or physical health will be delivered from its present danger.

III. The physician has a right to kill the child in order to save the mother's life or in order to prevent serious impairment of her mental or physical health.

Let us postpone for a moment the discussion of the third proposition and turn to the first two propositions. When Hirst formulated the principle we have quoted, justifying therapeutic abortions, physicians in general were much more confident that they could say of a tuberculous mother, or one suffering from cardiac disease, or eclampsia, etc.: Unless this pregnancy is terminated promptly the mother will die.

Formerly therapeutic abortions were frequently undertaken in heart disease, tuberculosis, and eclampsia. But at the present day we may say that heart disease does not in itself indicate a termination of pregnancy before a viable child can be delivered. Thus, for example, Fitzgerald⁶ reports the management of 126 women with heart disease during 192 pregnancies without the death of a single patient in pregnancy or labor.

The final conclusion of a very exhaustive study was that there is no evidence that tuberculosis is aggravated by pregnancy.⁷

Fovassier says in regard to abortions when the mother is tuberculous that the value of this procedure has not been certainly demonstrated at the Baudelocque Clinic and that "The sacrifice of the children is certain. The benefit to the mother is very often problematical."⁸

McNeile has pointed out that medical treatment of eclamptic patients has a much lower maternal mortality than the termination of pregnancy by therapeutic abortion.⁹

As to mental cases, Cheney says: "There appears to be no individual neurologic or psychiatric disorder that is an absolute indication for abortion in women suffering from such disorders"¹⁰ and experience shows that patients with severe neurologic and mental diseases may go through pregnancy and have healthy children.

And so with the development of new methods of treatment and with the attempt made by various physicians to follow an expectant policy and treat the disease from which a pregnant woman might be suffering until a viable child might be delivered, it has become more and more evident that pregnancy may go on to term in spite of serious mental and physical disorders of the mother, and she may suffer no detriment or even improve by reason of the pregnancy, and a healthy child will be born at term.

United States has been denied by the Supreme Court.¹⁵ But some countries have already reverted to a condition in which the will of a dictator can at any time decide who is to live and who must die. And there are those in our own country, a small minority let us hope, who would cast off our ancient principles of law and order and set up instead a regime which no longer recognizes the solid foundations of American liberty, but subjects the individual to the whims of a dictator.

In these days, therefore, it becomes a supreme duty to reaffirm the dignity of the human person, who has a right to life, liberty, and the pursuit of true happiness, of which he cannot be deprived except as a punishment for heinous crime of which he has been convicted by due process of law.

REFERENCES

- (1) Quoted by *Cheney, Clarence O.*: J. A. M. A. 103: 1914, 1934, from *Hirst, B. C.*: A Textbook of Obstetrics, Philadelphia, 1906. Cheney says: "This statement by Hirst is quoted as one setting forth, in my opinion, the fundamental principles to be considered in therapeutic abortion." (2) *De Lee, Joseph B.*: The Principles and Practice of Obstetrics, ed. 6, 1933, p. 1112. (3) Philadelphia, 1937, p. 176. (4) *Moore, T. V.*: Principles of Ethics, Philadelphia, 1937, pp. 177-178. It is worth mentioning here that a child may develop normal mentality after the whole left hemisphere was lost as a result of traumatic porencephaly, having its origin in a fall from a window when three years of age. *Kopp, J.*: Deutsche. Ztschr. f. Chir. 116: 226, 1912. (5) *Bouscarén, T. Lincoln*: Ethics of Ectopic Gestation, Chicago, 1933. (6) *Fitzgerald*: AM. J. OBST. & GYNEC. 29: 53, 1935. (7) *Fritz Schultze-Rhonot and Karl Hansen*: Ergebn. d. ges. Tuberk.-Forsch. 3: 344, 1931. (8) *Fovassier, A. P. H.*: L'avortement médicalement provoqué chez la femme atteinte de tuberculose pulmonaire chronique (thèse), Paris, 1936. (9) *Mcneile, Lyle G.*: J. A. M. A. 103: 548, 1934. (10) *Cheney*: J. A. M. A. 103: 1918, 1934. (11) *Taussig, Frederick Joseph*: Abortion Spontaneous and Induced, St. Louis, 1936, p. 386. (12) *Op. cit.*, p. 414. (13) *Haugwitz, Elfriede*: Über die Morbidität und Mortalität bei Kuenstlicher Schwangerschaftsunterbrechung. (Diss. Königsburg) 1935, p. 5 reports 4 deaths in 244 cases, and 23 in which the basic disease was aggravated. (14) *Taussig, Frederick J.*: Abortion Spontaneous and Induced, St. Louis, 1936, The C. V. Mosby Co., p. 414. (15) *Pierce*: Governor of Oregon, et al. v. Society of Sisters, 268 U. S., 510.

CATHOLIC UNIVERSITY OF AMERICA

Edwards, Mary S.: Premarital Examination Laws in Operation, J. Soc. Hyg. 26: 217, 1940.

Premarital Examination laws requiring syphilis tests to be made on both parties have now been in operation for periods ranging up to four years (Connecticut, Jan. 1, 1936). Thus data of considerable importance and interest are beginning to be collected.

Reports of over 600,000 blood tests received from 13 states show an incidence of 1.4 per cent positive for syphilis. A very high percentage of these infected persons (75 to 90 per cent) were unaware of their infection. In one state, in which the premarital examination law has been operating for several years, the number of babies reported as born with congenital syphilis has dropped 50 per cent.

The 20 states now requiring that both parties to a marriage license have a premarital examination for syphilis comprise between 50 and 60 per cent of the population of the country. Statistical calculations suggest that 1 in 35 marriages is endangered by syphilis.

HUGO EHRENFEST.

But, you may say, such statements are true in general. Suppose an individual case with all its attending circumstances in which the physician feels perfectly confident

- a. that a therapeutic abortion will not endanger the mother's life.
- b. that unless an abortion is performed and a nonviable child expelled from the uterus, the mother will certainly die.

May the physician under these circumstances perform a therapeutic abortion in order to save the mother's life?

One might answer such a question by merely saying that, as a matter of fact, no physician can ever be certain that the mother will not die from a therapeutic abortion or that she will certainly die unless it is performed. But the question raises the problem whether or not the physician is ever justified in taking a human life, directly and by explicit intention, and this problem is fundamental in the whole discussion.

Let us turn to the consideration of this problem.

Has any man a right to kill one man in order that another may live? Suppose an observer watching two men struggling for a life preserver. Both sink when both have hold of it, but it can support either alone. The man on shore has a rifle. Suppose he says: If I don't shoot one, both will die. Therefore, it is not only justifiable but also my duty to kill one that the other may live. You would perhaps recoil from the exercise of any such duty and say to yourself: By what authority have I become the arbiter of life and death in human affairs? Man has a right and a duty to use his own life to good purpose, but no right to do away with himself or kill another human being.

But one might say: In regard to the child and the mother, the life of the mother is of so much more value than that of the child, and so the figure of the men struggling for the life preserver is not an appropriate comparison. But who can look into the future and say the life of a child is of so much less value than that of its mother? And suppose you say that one of the men in the water was a worthless tramp and the other a gentleman of importance, would you be justified in shooting the tramp in order to save the life of the gentleman?

A physician has a clear duty to preserve human life, but by what principle can one demonstrate that he is the arbiter of life and death and can therefore decide to kill one human being in order that another may live?

When we approach the consideration of the rights of one human being over the life of another, we are confronted with a problem where the principles we may enunciate may have consequences that will soon extend much further than we think, and lead to results that we would abhor.

Have the parents a right to say whether or not a child shall live and, if so, is it lawful for the physician to act as their executioner when they decide that, all things considered, it is better for the child to die?

If the parents have this right, is it also to be conceded to the state and, if so, under what circumstances? The modern state claims a right over the child higher than that of the parents, a claim which in our

This latter group comprised the special and specific condition in which we became interested. We attempted to find out how often women with a primary progressive tuberculosis of the lungs would show an isolated clinically latent tuberculosis of the endometrium. Consequently, in this study, we eliminated women with tuberculosis of the lungs and associated manifest, chronic, probably tuberculous inflammation of the adnexa, and have examined only women with evident progressive tuberculosis of the lungs, and with no clinically manifest inflammatory process of the ovary or tube. Our material consists of 134 biopsies obtained from 125 female patients in the tuberculosis division of the Cook County Hospital, the entire group showing radiologic and laboratory evidence of active pulmonary tuberculosis. In each of these women endometrial strips were obtained, using the suction curet described by Randall. There is no question that occasionally the amount of tissue obtained is so small that pathologic analysis furnishes meager information. Consequently, only positive findings should be accepted for final conclusions; negative findings have no necessary significance. However, it may be expected that an endometrium which is active throughout, soft and proliferating, or which is in the process of developing multiple tuberculous nodes, would give evidence of its physiologic or pathologic characteristics even though, by suction curettage, but a small piece of tissue is obtained. Rock, in a recent study involving the role of endometrial biopsy in diagnosis, has found four, apparently latent, cases of tuberculosis of the endometrium.

With this restriction borne in mind, then, it may prove of interest that we found in the 125 women only two cases of manifest endometrial tuberculosis. The histories of these cases are as follows:

CASE 1.—M. K. (Hosp. No. 360-1233, 265), a 39-year-old colored female, was admitted to Cook County Hospital on Jan. 12, 1939, with the complaints of malaise, weakness, and cough of three weeks' duration. She had been in a poor state of health (severe secondary anemia) for the past twelve years. Present illness was ushered in by an upper respiratory infection characterized by marked weakness and expectoration of a whitish phlegm.

Past history was essentially negative except for the usual childhood diseases. The menarche had occurred at 13 years, every 28 to 30 days, of five days' duration; flow moderate; no pain. Amenorrhea had been present from birth of her last baby in May, 1938 to January, 1939. Patient was a gravida v, para vi. There was one set of twins. Her oldest child was 17 years of age. Last menstrual period occurred on Jan. 2, 1939.

Family history was essentially negative. Inventory by systems likewise was negative.

Physical examination revealed a poorly nourished adult female. Temperature was 101.8° F., pulse 108, and respiration 27. Lungs showed increased tactile and vocal fremitus on left side with decreased resonance. There were moist râles through entire left chest with patch of cavernous breathing posteriorly. Heart and abdomen were negative. Pelvic examination showed a parous introitus, and relaxed pelvic floor. The vulva and vagina were negative. There was a moderate cystoectocoele; the corpus erect and of normal size; adnexa not palpably enlarged, fixed, or tender; cervix appeared normal.

X-ray examination of the chest on Jan. 13, 1939, was diagnostic of a tuberculous pneumonic consolidation of the left chest; tuberculosis organisms were recovered from the sputum, and patient was transferred to the Tuberculosis Hospital, where

THE COINCIDENCE OF TUBERCULOSIS OF THE ENDOMETRIUM WITH TUBERCULOSIS OF THE LUNG*

JULIUS E. LACKNER, M.D., WALTER SCHILLER, M.D., AND
ALEX S. TULSKY, M.D., CHICAGO, ILL.

*(From the Departments of Obstetrics and Gynecology of the Michael Reese Hospital
and the Department of Pathology of the Cook County Hospital)*

DURING the past year, we have studied the endometrium in a group of women suffering from pulmonary tuberculosis in the tuberculosis division of the Cook County Hospital. Our aim was to determine what, if any, effect a pulmonary tuberculosis has upon the endometrium. It appears that tuberculosis of the endometrium is almost impossible to diagnose clinically. One of us (W. S.) has observed that of many thousands of curettings submitted to pathologists in the course of twenty years, a case of tuberculous endometritis has never been sent in with a diagnosis of this condition made by the clinician.

The literature is replete with case reports of tuberculous endometritis. Daniel reports a case of tuberculosis of the uterine body with no adnexal involvement. Ferroni describes a similar case occurring in an 18-year-old nullipara, the presenting complaint being metrorrhagia. Simon, Cullen, Williams, Diethelm, Heinrich, and Reinhart likewise cite cases of tuberculous endometritis unassociated with adnexitis. Bungeler reports the appearance of an acute miliary tuberculosis following curettage for a tuberculous endometritis, and warns against such a procedure in these cases lest a similar mishap occur. Reinhart adds that the lesion may be primary or secondary, the latter being the more common of the two. Histologically, they differ in that the primary type appears as a small, discrete, sharply-defined lesion composed almost exclusively of epithelioid cells, with involvement of regional lymph nodes. The secondary type is usually greater in area, less sharply-defined, variable in component elements, and does not heal readily. Dickinson is of the opinion that infection of the uterus takes place through the blood stream from a distant focus, through the lymphatics from an adjacent focus, or by direct extension.

The general impression is confirmed that no curettings are sent to the pathologist with the clinical diagnosis of tuberculous endometritis. Some of these cases suggest a chronic adnexitis, or, even more frequently, some disturbance of the menstrual cycle, and in most cases the diagnosis is made only (1) after a curettage, (2) after examination of the removed organs, or (3) upon autopsy. While the majority of lesions appear in the age group of 16 to 36 (Reinhart and Moore), Biggs has reported a case of tuberculous endometritis in a 20-month-old infant (as an exception to the above).

Clinically, two groups of tuberculous endometritis may be distinguished. First, the involvement associated with progressive tuberculosis of the ovaries, the tubes, or both, the endometritis representing only an associated pathologic process of minor clinical importance. Second, tuberculosis of the endometrium with normal tubes and ovaries, associated with and developing from a tuberculous infection of an organ outside of the pelvis, as for example, the lungs, and the mesenteric or hilar lymph nodes, this representing an important and obviously unsuspected syndrome of primary extragenital tuberculosis.

*Presented at a meeting of the Chicago Gynecological Society, April 19, 1940.

Past history: She had diphtheria when a child. Menses began at 13 years of age, irregular every four to six weeks, of two days' duration, flow scanty, no pain. Cervical amputation for cystic hypertrophic cervix was done in 1935. Last menstrual period occurred on May 20, 1939.

Family history was negative.

Inventory by systems was essentially negative.

Physical examination revealed a poorly nourished adult female. Temperature 97.2° F., pulse 84, respiration 24. Head and neck were negative. X-ray picture revealed infiltrative changes throughout both lungs, most pronounced in the upper halves, with bilateral cavitation. Remainder of general examination was negative. Pelvic examination was as follows: Parous outlet with relaxed floor; slight cysto-rectocele; corpus uteri in retroversion but not fixed. The adnexa were freely movable and normal; cervix not present (removed by operation). Sputum was positive for *B. tuberculosis*. White blood count was 8,200, red blood count 3,870,000. Hemoglobin 70 per cent. Urine negative. Serology negative. Weight varied from 100 to 80 pounds in course of illness. No therapy was carried out. Endometrial biopsy was obtained June 16, 1939.

DISCUSSION

It can be seen by the protocols of the above cases that the history and clinical findings resemble to a large extent the history and clinical findings of most of the cases of tuberculous endometritis gleaned from the literature. That is, they are characterized by an extreme paucity of leading pelvic symptoms and of clinical and laboratory findings. Both patients apparently had normal or almost normal menstrual cycles. They had no gynecologic complaints and by the same token vaginal examination was completely negative in one case and elicited minimal findings in the second case. Neither of these cases had a vaginal discharge. This instance of two cases among 125 corresponds to an incidence of about 1.60 per cent. This harmonizes with the figures obtained from the autopsy records of the Cook County Hospital during the last ten years. In this period of time about 13,000 autopsies have been performed. Roughly, three thousand of these were done on adult women. Of this group, 113 had pulmonary tuberculosis. In the 113 cases there were two instances of tuberculous endometritis without adnexitis (1.77 per cent). There were two cases of tuberculous adnexitis and associated tuberculous endometritis (1.77 per cent). There were six cases of tuberculous salpingitis (5.31 per cent), and hence four cases of tuberculous adnexitis without tuberculous endometritis. Among 107 cases of women with tuberculosis of the lung without tuberculosis of the adnexa there were two cases of isolated tuberculous endometritis. There were then 1.87 per cent of cases of isolated tuberculous endometritis in the autopsy material as compared with 1.60 per cent in our clinical material.

From the pathologic point of view we may use the classification which Ghon has given for the genesis of genital tuberculosis in women. Tuberculosis of the endometrium, according to its localization, never is a primary condition. In secondary tuberculosis with (1) endogenous spread we must distinguish between (a) a generalization of the infection, with the local tuberculosis representing only a part of the generalized infection or (b) an isolated hematogenic focus or metastasis. The second type of secondary tuberculosis (2) has been called by Ghon "reinfection," represented by cases of a new infection in some other organ after the organism has developed a primary focus in one organ. Pozzi called

a diagnosis of far-advanced bilateral pulmonary lesion was made. Her weight was 84 pounds. Serology was negative, white blood count, 7,200, red blood count 3,900,000. Hemoglobin 70 per cent. Urine negative. Sputum persistently was positive. No therapy could be carried out. Endometrial biopsy was obtained Jan. 26, 1939, and biopsy of the endocervix on Feb. 15, 1939. There were no pelvic complaints at any time.



Fig. 1.



Fig. 2.

Fig. 1.—(Case 1.) Endometrium from suction curettage. Numerous small tubercle nodes, most of them with typical Langhans' giant cells. Magnification $\times 60$.

Fig. 2.—(Case 2.) The same section as in Fig. 1 under higher power.



Fig. 3.—(Case 2.) Endometrium from suction curetting. Left side, cystic hyperplasia. Right side, small caseating tubercle in the cytogenic tissue. Magnification $\times 60$.

CASE 2.—M. S. (Hosp. No. 360-1233, 83), a 43-year-old white female, para iii, gravida iii, was admitted to the tuberculosis division of Cook County Hospital on June 2, 1939, with complaints of cough, expectoration, weight loss, weakness, and dyspnea of four months' duration. This was initiated by a severe cold characterized by hemoptysis over a period of several weeks, and marked weakness,

dently the authors have segregated a group of patients suffering from tuberculous lesions and investigated the endometrium; and from their report we assume that in patients without palpable adnexal swelling, we can find tuberculous lesions in the endometrium in about one out of fifty or sixty. A question which comes to my mind is: What happened later to these 134 patients after the diagnosis had been made? Suppose we made a positive diagnosis of tuberculous endometritis, what are the results of the disease? What goes on following the discovery of the tuberculous endometritis and what is done with the patient? Does the infection spread from the endometrium to the adnexa or has it come from the adnexa to the endometrium? I do not believe that any one has much knowledge concerning these things.

This thesis has also brought up the question, Do we as gynecologists have a right to inspect these tissues? What about the other specialists and what will happen to the patients in our institutions? I think we will have to be cautious about going too far.

DR. A. G. GABRIELIANZ.—I would like to ask if the von Pirquet test was used in cases of primary tuberculosis of the internal genital organs? Was the diagnosis confirmed by operation?

DR. WALTER SCHILLER.—The cases of so-called tuberculosis of the cervix were discovered by direct inspection through a speculum, and I do not know whether a von Pirquet test was done.

The textbooks generally mention two types of tuberculosis of the endometrium only, one in which the tuberculosis of the endometrium is associated with a tuberculosis of the tube and eventually of the ovary, and the second in which the tuberculosis of the endometrium is part of a generalized hematogenic tuberculosis. Our cases deal with a localized hematogenic tuberculosis of the endometrium which evidently did not produce local symptoms.

DR. J. P. GREENHILL.—Dr. Galloway's facetious remarks may lead us to believe that the work of Dr. Lackner and his associates has only a theoretical interest because, even if women with active pulmonary tuberculosis have endometrial tuberculosis, nothing will be done about it. It seems to me that the reverse of this question is important. As gynecologists, we are interested in knowing how many women with genital tuberculosis have pulmonary tuberculosis at the same time.

My interest in this subject is more than academic, because many years ago I studied 200 cases of proved genital tuberculosis. In this series at least 25 per cent of the women had pulmonary tuberculosis. The actual incidence of pulmonary involvement was undoubtedly higher.

In my series of 200 cases of genital tuberculosis, the tubes were involved in all the cases and the uterus in more than 70 per cent. The generally accepted impression is that nearly all cases of tuberculous endometritis are secondary to tubal tuberculosis. As Dr. Schiller has suggested, in rare cases the tuberculous endometritis may be primary and the tubal infection secondary.

this type of reinfection "primitive secondary tuberculosis" and differentiated between reinfection developing from the organism itself and a reinfection from the outside. Tuberculosis of the endometrium, in our cases, must be classified as secondary tuberculosis of the Type b. It represents not the part and component of a generalization, as in a miliary tuberculosis, but an isolated metastasis, so to speak, of the primary pulmonary process. So far as the method of spread is concerned, by exclusion we must accept the hematogenic route. It may be similar to the spread of a miliary tuberculosis, the difference being that the tubercle bacilli circulating throughout the organism found a favorable nidus only in the endometrium. Ghon quoted as an example of this type of secondary tuberculosis, hematogenic salpingitis. The possibility of the occurrence of an isolated hematogenic tuberculous endometritis would appear to be proved by our findings.

We wish to take this opportunity to thank Dr. Mendelssohn for permitting us to use the patients on his service in the tuberculosis division for this study.

REFERENCES

- (1) Biggs, G. P.: Proc. N. Y. Path. Soc., p. 259, 1901.
- (2) Bungeler, W.: Frankfurt. Ztschr. f. Path. 47: 313, 1935.
- (3) Cullen, T. S.: Johns Hopkins Hosp. Rep. 4: 1894-1895.
- (4) Daniel, C.: Rev. franç. de gynéc. et obst. 20: 305, 1925.
- (5) Idem: Ibid. 24: 220, 1929.
- (6) Idem: Gynéc. et obst. 11: 161, 1925.
- (7) Depkin, H.: The Menstrual Cycle in Tuberculous Adnexitis, and a Discussion of the Pathogenesis of Uterine Tuberculosis, Inaug. Diss. Rostock, 1920.
- (8) Dickinson, A.: Am. J. Surg. 11: 558, 1931.
- (9) Diethelm, M. W., and Ramsay, T. L.: Am. J. Obst. & Gynec. 30: 420, 1935.
- (10) Ferroni, E.: Zentralbl. f. d. ges. Geburtsh. u. Gynäk. 2: 19, 1924.
- (11) Fruhinsholz and Feuillade: Gynéc. et obst. 10: 305, 1924.
- (12) Gerich, Obokar: Monatschr. Geburtsh. u. Gynäk. 70: 278, 1925.
- (13) Ghon, A.: Wien. med. Wchnschr. 44 & 45, 1922.
- (14) Idem: Genesis of Genital Tuberculosis in Women. Vorträge des Ersten Ärztlichen Special Kurses für Frauen u. Herzerkrankheiten in Franzenbad, September, 1922.
- (15) Gragert, Otto: Beitr. z. klin. d. Tuberk. 63: 768, 1926.
- (16) Gummert, G. L.: Gynéc. et obst. 8: 347, 1923.
- (17) Hartmann-Keppel, G. L.: Monatschr. f. Geburtsh. u. Gynäk. 17: 1242, 1903.
- (18) Hussy, P., and Vetter, H.: A.: Am. J. Obst. & Gynec. 23: 579, 1932.
- (19) Kunderat: Arch. f. Gynäk. 65: 87, 1912.
- (20) Mayer, A.: Beitr. z. d. Tuberk. 63: 874, 1926.
- (21) Moore, R. A.: J. Lab. & Clin. Med. 14: 413, 1929.
- (22) Reinhardt, G. L., and Schroder, R.: Monatschr. f. Geburtsh. u. Gynäk. 55: 15, 1921.
- (23) Reeb: Bull. Soc. d'obst. et de gynéc. 14: 267, 1925.
- (24) Rock, J.: Am. J. Surg. 48: 228, 1940.
- (25) Nordwest-deutsche Ges. f. Gynäk. u. Geburtsh. 2: 10, 1920.
- (26) Simon, Felix: On the Symptoms of Open Uterine Tuberculosis, Inaug. Diss. Giesen, 1920.
- (27) Schellenberg: Zentralbl. f. Gynäk. 56: 2105, 1932.
- (28) Schlumpert: Arch. f. Gynäk. 94: 867, 1922.
- (29) Stewart, C.: J. Obst. & Gynaec. Brit. Emp. 40: 299, 1933.
- (30) Schroeder, E.: Deutsche med. Wchnschr. Leipzig and Berlin 1903, 29 Ver.-Beil., 138.
- (31) Franque, P.: Prag. med. Wchnschr. 50: 653, 1906.
- (32) Weibel, W.: Tuberculosis of the Female Genital Apparatus, Halban-Seitz. 5: pp. 329 and 353.
- (33) Williams, P. R.: Am. J. Obst. & Gynec. 6: 230, 1923.

DISCUSSION

DR. CHARLES E. GALLOWAY.—My knowledge of tuberculous endometritis is purely academic, and I do not consider myself an authority because I have had no experience with it. It seems to me that this subject opens up a very interesting field of research that so far has not been covered. If these patients in the various county institutions who are suffering from tuberculosis can be used for investigative purposes without harm to the individual patient, I believe we are justified in doing so. No one knows anything about the early stages of tuberculous endometritis as the authors have described it. I should like to emphasize one of the points brought out, namely that negative findings are of no value, although positive findings are of some importance. Evi-

To make possible even a rough evaluation of the effect of paraldehyde, other types of medication, such as morphine or barbiturates, were excluded. However, the majority of patients required an anesthetic during delivery. Nitrous oxide was used in most instances, novocaine (local or caudal) in several cases, and chloroform in one case. Ether was not used, as its presence in the blood would have interfered with the determination of paraldehyde.

In collecting the blood specimens a necessary precaution is to avoid the use of alcohol sponges in cleansing the arm. Alcohol, like ether and acetone, is a volatile oxidizable substance and interferes, therefore, with the determination of paraldehyde. Cotton sponges moistened with mercury bichloride solution were employed instead.

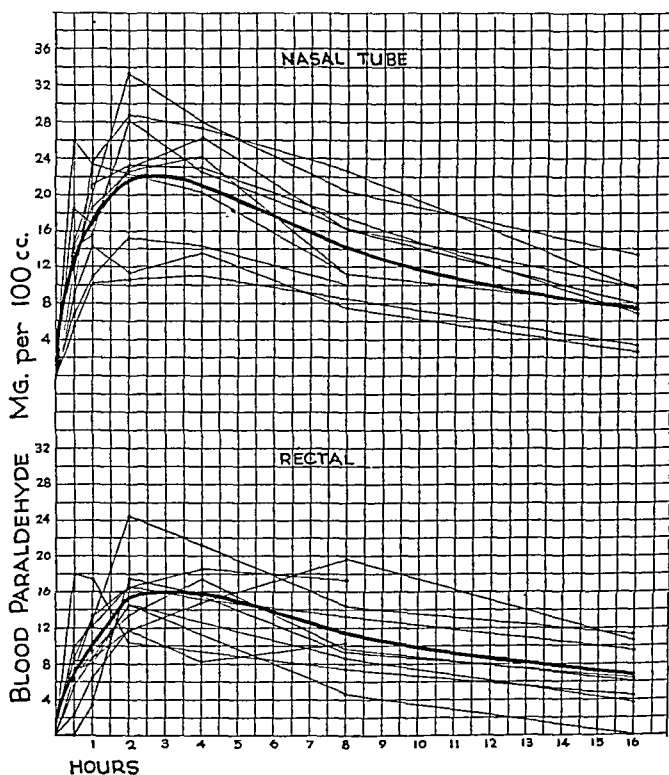


Fig. 1.—Concentrations of paraldehyde in the blood following its administration in patients during labor. Dose: 30 c.c. of paraldehyde in 60 c.c. of olive oil. Thin lines represent individual cases. Heavy lines represent average values obtained following rectal and gastric (nasal tube) administration, respectively.

PROCEDURE

The routine procedure consisted in obtaining a specimen of blood for a blank determination immediately before administration of the paraldehyde, and additional specimens at $\frac{1}{2}$, 1, 2, 4, 8, and 16 hours after administration. Oxalate was used as anticoagulant. A sample of cord blood was obtained in most instances. All specimens were kept in tightly stoppered vials in the refrigerator until ready for analysis by the method of Levine and Bodansky.⁹

RESULTS

The results are represented by the two sets of curves in Fig. 1. From these curves it is seen that individual variations were marked, but that, in general, the

CONCENTRATION OF PARALDEHYDE IN THE BLOOD FOLLOWING ITS ADMINISTRATION DURING LABOR*

HERMAN L. GARDNER, M.D., HARRY LEVINE, PH.D., AND
MEYER BODANSKY, PH.D., M.D., GALVESTON, TEXAS

(From the Departments of Obstetrics and Gynecology and Pathological Chemistry, University of Texas School of Medicine, and the John Sealy Memorial Research Laboratory)

PARALDEHYDE for producing analgesia and amnesia in obstetric deliveries was introduced by Rosenfield and Davidoff¹ in 1932. Since then many reports have been published concerning the value of this drug, when given either alone or in combination with other drugs, such as benzyl alcohol, sodium pentobarbital, morphine, sodium amytal, and ether. A review of these contributions is not essential in this connection in view of the summary of the literature by Bushnell.² Here it suffices to state that paraldehyde appears to be a comparatively safe drug as regards both mother and fetus.^{3, 4} However hypersusceptibility to the compound has been encountered,⁵⁻⁷ and in two known instances^{5, 7} the result was fatal.

Owing, possibly, to the relative infrequency of untoward effects, little attention has been given to this aspect of the problem, so that the use of paraldehyde is, in some respects, still empirical. Thus, we find no published data concerning the concentrations of paraldehyde in the blood following its administration to subjects in labor. Such data may be expected to be of value in defining the concentrations required to produce a desired degree of amnesia and analgesia and in indicating deviations in the metabolism of paraldehyde associated with certain complications, such as eclampsia and liver disease.⁸ It is to be realized that the effect of a given dose of paraldehyde may be quite variable in different individuals.

In view of these circumstances it seemed desirable to investigate the concentrations of paraldehyde present in the blood of parturient women at intervals following administration of the drug. The present report is based on the results in 20 patients who were given a single dose of 30 c.c. of paraldehyde in 60 c.c. of olive oil. In our experience the use of olive oil lowered the rate of absorption and assured a more prolonged effect. Ten of the patients received the drug by rectal injection; the others were given the paraldehyde-olive oil mixture by the nasal tube route. The paraldehyde was administered when the cervix showed a dilatation of approximately 3 cm., or more, and when forceful contractions were occurring at intervals of about three to five minutes. Patients who either expelled or vomited a portion of the drug have not been included in this report.

*This work was supported partly by a grant from the Committee on Therapeutic Research (No. 383), Council on Pharmacy and Chemistry, American Medical Association.

to 8.8 to 12.6 mg. per 100 c.c. In one instance the mother received nitrous oxide anesthesia; in the others a local anesthetic was used. No delay in respiration was observed in four other infants in our series, with cord blood values of 8.8 to 11.8 mg. per 100 c.c., and who were delivered without anesthetics. Kotz and Kaufman⁴ investigated the effect of paraldehyde analgesia on the onset of respiration and found this to be definitely delayed. The average for 100 babies whose mothers received paraldehyde was 39.5 seconds, compared to an average of 9.8 seconds for a similar group whose mothers received no analgesia. This slight delay in initial respiration was not considered to have any injurious effect on the baby (see also Colvin and Bartholomew³).

TABLE I. CONCENTRATIONS OF PARALDEHYDE IN CORD BLOOD AND MATERNAL BLOOD AT DELIVERY

PATIENT	CORD BLOOD MG. PER 100 C.C.	MATERNAL BLOOD MG. PER 100 C.C.
1n*	27.2	28.8
3n	24.4	25.2
5n	24.1	26.7
6n	11.8	11.0
7n	12.6	12.6
10n	17.8	21.0
1r	18.7	15.6
2r	8.8	12.0
3r	7.7	8.3
4r	9.6	14.5
6r	12.3	13.8
7r	14.2	13.9
8r	8.8	12.6
Averages	15.5	16.6

*n, denotes that the paraldehyde was given by nasal tube; r, that it was given rectally.

SUMMARY

The concentration of paraldehyde in the blood was determined in parturient women at intervals ($\frac{1}{2}$, 1, 2, 4, 8, and 16 hours) following rectal, or oral (nasal tube) administration of 30 c.c. of paraldehyde in 60 c.c. of olive oil.

The highest and lowest maximum concentrations attained in 10 patients who received the drug rectally were 24.4 and 11.8 mg. per cent, respectively. Six of these subjects experienced a period of complete amnesia, varying from two to ten hours.

In 10 patients who received the drug orally, the highest and lowest maximum concentrations were 33.2 and 11 mg. per cent, respectively. The patient with the highest blood paraldehyde curve experienced complete amnesia for ten hours. The patient with the lowest curve experienced little or no amnesia, although her pains were lessened.

All patients in whom the blood paraldehyde rose to 20 mg. per 100 c.c., or above, and some who did not attain this level, experienced a period of complete amnesia.

Analyses of 13 cord blood specimens revealed that at the time of delivery the concentration of paraldehyde in the fetal circulation approximated that in the maternal blood. The averages for the entire group were: 15.5 mg. per cent for cord blood; 16.6 mg. per cent for maternal blood.

concentrations of blood paraldehyde were higher when the drug was given orally than when given rectally. A comparison of the curves representing the mean values (heavy lines) shows that the maximum concentrations of paraldehyde in the blood following rectal administration were on the average 70 to 75 per cent of the values obtained following oral administration.

As shown in Fig. 1, the highest maximum level for the 10 individual curves in the "rectal" group was 24.4 mg. per cent. In this case the patient had complete amnesia for seven hours, the amnesia beginning about twenty minutes after administration of the paraldehyde and lasting until two hours before delivery. The lowest maximum level for this group was 11.8 mg. per cent. In this case, the patient experienced no amnesia, although the pains were much relieved.

The highest and lowest maximum concentrations obtained by the "nasal tube" (oral) method were 33.2 and 11.0 mg. per cent, respectively. The patient with the high blood paraldehyde curve experienced complete amnesia for ten hours, delivering five and one-half hours following administration without requiring any other anesthetic. On the other hand, the patient with the low paraldehyde curve obtained little or no amnesia, though her pains were apparently lessened. She delivered, under local anesthetic, five and three-fourths hours following administration of the paraldehyde. The remaining 8 patients in this group experienced complete amnesia for periods varying from four and one-half to eleven hours.

Of the 10 patients who received the drug by the rectal route, 6 experienced a period of complete amnesia, varying from two to ten hours, the average being six hours. Three patients, with maximum blood paraldehyde levels of 11.8, 14.5, and 19.7 mg. per cent, respectively, experienced no amnesia. One patient with a maximum blood level of 17.5 mg. per cent had partial amnesia.

No patient in either group in whom the blood paraldehyde concentration rose to 20 mg. per 100 c.c., or above, failed to experience a period of complete amnesia. However the possibility is recognized that the level of consciousness is quite variable and that in some individuals a higher concentration than 20 mg. may be required to produce amnesia. One such case has been encountered since completing the present series of observations.

Where complete amnesia occurs, the onset is usually within fifteen to thirty minutes after the drug is given. This is of interest in view of the observation that the blood paraldehyde level at thirty minutes was frequently lower than later when the amnesia had been abolished. Almost invariably the concentration at the end of the period of amnesia was higher than at the beginning of amnesia. These relations are at present under investigation, the working hypothesis being that a high concentration of paraldehyde is attained in the brain soon after absorption of the drug begins and that this determines the onset and degree of narcosis. In view of the solubility of the drug in lipoids, it may be assumed that its distribution between the blood and tissues is such that large amounts accumulate in organs such as the brain and liver which are rich in lipoid material. As the concentration in the brain diminishes, the narcotic effect disappears.

The concentration of paraldehyde was determined in 13 specimens of cord blood. In two instances blood was obtained simultaneously from the mother. The results in these cases, cases 1n and 3r, are included in Table I. In the other instances, it was necessary to derive the values for the concentration in the maternal blood at the time of delivery by referring to the respective blood paraldehyde curves. The data thus obtained are likewise given in Table I. It will be noted that in the majority of instances the values for cord and maternal blood were in fairly close agreement. The averages for the entire group were: 15.5 mg. per cent for cord blood; 16.6 mg. per cent for maternal blood.

In passing it may be noted that the three infants in our series with the highest cord blood paraldehyde values (24.1, 24.4, 27.2 mg. per 100 c.c.) exhibited no unusual symptoms; none showed the slightest degree of apnea. Delivery in these cases occurred without other anesthesia. Apnea was observed in three other infants (two of these were premature) in whom the cord blood paraldehyde amounted

reviewed, positive evidence for the diagnosis of genital tuberculosis could not be obtained in 6 instances, because no tissue was available for microscopic examination.

Several of these patients came to us after a gynecologic operation elsewhere with the complaint of a draining sinus from an old surgical scar in the lower abdomen, and with a diagnosis of tuberculous peritonitis. Some were operated upon at our hospital, but at the time of operation, due to the fact that the genitalia together with a portion of the peritoneal cavity were involved by some indefinite infection, only a small section of omentum or peritoneum was removed for biopsy, which was reported later by the pathologist to be tuberculosis.

Because there is lack of definite proof by biopsy as to the existence of tuberculosis of the genitalia in these 6 cases, they have been excluded from this report and only the remaining cases, 15 in number, have been analyzed for presentation here.

All of our patients were in the "childbearing age" group. Twelve of the 15 (80 per cent) occurred in women between the ages of 20 and 30, two between the ages of 31 and 35, and the remaining patient was 43 years old. However, it is felt that the average age should be lowered considerably since all of the patients undoubtedly had been afflicted with tuberculous involvement of the genitalia before its discovery by surgical intervention. Many of the patients attending our outpatient department clinic had gynecologic complaints long prior to operation, and these complaints, we feel, if properly interpreted would have led to an earlier diagnosis.

A history of menstrual disturbance as described by some writers was not a significant factor in our study. The only finding considered of some value was the disclosure that 6 of the series, or 40 per cent, had begun to menstruate between the ages of 15 and 17 years, which is somewhat later than the average. The onset of menses in the remaining patients was earlier, one beginning at eleven years of age.

Four, or approximately 26.5 per cent, were sterile, although only one of these actually complained of sterility. Two others gave a history of one pregnancy with early abortion. Three of the series were single while 6 had families ranging from one to six children.

Various investigators have reported the existence of pulmonary tuberculosis in from 50 per cent to 90 per cent of patients with genital tuberculosis examined at autopsy.² On the other hand, King³ in a review of 26 cases of pelvic tuberculosis, points out that only 6 of his series showed evidence of pulmonary involvement and states that "it is clear that the extent of pulmonary involvement plays at most but a small part." This is definitely in keeping with our findings, in that 12 of the 15 cases reported in this paper had negative chest x-rays or were considered chest-negative clinically. Only 3 showed signs of pulmonary tuberculosis.

Very enlightening is the fact that in not even one instance was the diagnosis of genital tuberculosis correctly made or even considered pre-operatively, the usual diagnosis being tuboovarian abscess, acute or chronic salpingo-oophoritis, pelvic cellulitis, appendicitis, etc. More important still is the disclosure that in only one case of the entire series was the diagnosis made by the operating surgeon visualizing the gross pathology, the others being diagnosed microscopically.

The symptoms of tuberculous involvement of the female genitalia resemble closely those of chronic gonorrheal salpingitis. Pelvic examination is of very little assistance in differential diagnosis unless the patient is a virgin, in which case pelvic inflammation is a clue to the possible

REFERENCES

- (1) Rosenfield, H. H., and Davidoff, R. B.: *New England J. Med.* 207: 366, 1932. (2) Bushnell, L. F.: *Internat. Abst. Surg.* 67: 155, 1938. (3) Colvin, E. D., and Bartholomew, R. A.: *Internat. Clin.* 4: 191, 1938. (4) Kotz, J., and Kaufman, M. S.: *J. A. M. A.* 113: 2035, 1939. (5) Kotz, J., Roth, G. B., and Ryon, W. A.: *J. A. M. A.* 110: 2145, 1938. (6) Jenkins, J. L., and Herrod, J.: *Bull. John Sealy Hospital and University of Texas School of Medicine* 1: 27, 1939. (7) Stiles, J. A.: Personal communication to M. B. (8) Bodansky, M., Jenkins, J. L., and Levine, H.: (In press.) Levine, H., Gilbert, A. J., and Bodansky, M.: *J. Pharmacol. & Exper. Therap.* 67: 299, 1939; *Idem*: *Ibid.* 68: July, 1940. (9) Levine, H., and Bodansky, M.: *J. Biol. Chem.* 133: 193, 1940.

PELVIC TUBERCULOSIS

WITH A REPORT OF A CASE OF TUBERCULOSIS OF THE CERVIX

A. H. LAHMANN, M.D., F.A.C.S., AND S. F. SCHWARTZ, M.D.,
MILWAUKEE, WIS.

(From the Gynecological Service of the Milwaukee County General Hospital and
Department of Obstetrics and Gynecology of the Marquette University
School of Medicine)

TUBERCULOUS involvement of the female genitalia, although seemingly rare, is more prevalent than is generally assumed. The increased number of articles appearing in the literature has, in recent years, made for a much better understanding of this subject by the profession. However, few men have had enough individual experience with a sufficient number of cases to evaluate signs and symptoms as presented by the patient for adequate diagnosis, and treatment, which is still a largely controversial subject, remains a major problem.

Due to the fact that genital tuberculosis has been estimated to constitute from 5 to 8 per cent of all pelvic inflammatory conditions, it has of necessity become one of the important diseases to consider in the differential diagnosis of any affection of the female genitalia. However this is usually very difficult, and may be impossible on occasion, because the symptoms and signs are not typical and closely resemble those of numerous other maladies affecting the female genitalia.

Various investigators have found that genital tuberculosis is usually secondary to tuberculosis elsewhere in the body, and occurs most frequently in the years of active sex life. Also, there is a marked tendency for the disease to descend from the tubes to the endometrium, and it involves most commonly the organs in the order mentioned, namely: (1) tubes 90 per cent, (2) endometrium 75 per cent, (3) ovaries 30 per cent, (4) cervix 5.5 per cent, and vagina and vulva, 0.5 per cent.¹ There is no tendency for the disease to spread to the urinary tract.

MATERIAL

In the preparation of this paper, a study was made of 21 patients with tuberculosis involving the female genitalia. These patients were admitted and treated at the Milwaukee County General Hospital in the eleven-year period from January, 1929 to January, 1940. Of the cases

is considered by some to be a rather hazardous procedure because of the possibility of widespread dissemination of the tuberculous process following the use of the curet.

In our cases, the tubes were involved in 6 patients, the tube and ovary in 4, the ovary in 4, and the cervix in only one instance. This does not exclude the involvement of a greater number of structures, since in many instances the tubes, ovaries, or uteri were not removed and therefore not available for examination.

Since the literature stresses such a high percentage of uterine involvement, it is significant that there was endometrial involvement in not even one case of our series, although 4 uteri were available for careful microscopic examination.

Bishop⁶ reports a case of extensive destruction of the tubes and cervix without involvement of the endometrium or myometrium which in this instance tends to show a relative resistance of the endometrium to tuberculous infection. Danforth⁷ mentions the fact that Watson, in 1934, reported a similar case.

Tuberculosis of the ovaries is of much less frequency than that encountered in the tubes or uterus. Involvement is estimated at from 15 to 20 per cent of all cases of pelvic tuberculosis. However, involvement occurred in 8 of our cases, or 53.3 per cent, which demonstrated ovarian tuberculosis to be of far greater frequency than that occurring in the endometrium, and corresponds with the findings of Schmitz and Geiger,⁸ who place the endometrium after the ovaries in the order of their frequency of occurrence.

In only one case (6.7 per cent) was tuberculosis of the cervix encountered.

Tuberculosis of the cervix was first described in 1831 by Raynaud, and the literature since has contained numerous descriptions, with many authorities^{9, 7} reporting isolated cases. Collins¹⁰ in February, 1939, reported on a study of 191 cases available in the literature, 16 of which he considered to be primary tuberculosis of the cervix. A primary tuberculosis of the cervix can be considered only when no other focus of tuberculosis is demonstrable in the patient, and before a case is placed in this category "an exhaustive autopsy should have been performed to exclude the presence of an earlier tuberculous lesion."¹²

Tuberculosis of the cervix is usually associated with tuberculosis elsewhere in the body. Lester¹¹ states that 4 per cent of women who have tuberculosis elsewhere in the body exhibit this disease of the cervix. It is usually confused with carcinoma, syphilis, severe erosion, gonorrhea, sarcoma, and actinomycosis, and can be diagnosed definitely only by microscopic examination of the four pathologic forms mentioned below, the first two of which are most commonly seen. It seems that this classification really describes the various stages of the same pathologic process.¹²

1. Vegetative, this type surrounds the entire os and consists of a large fungating granuloma, bright red in color, which bleeds very easily.

2. Ulcerative type, which is the most common variety and appears as a large, deep, irregular, punched-out ulcer.

3. Miliary, the cervix has the appearance of implanted miliary tuberculosis.

4. Interstitial, the infection involves the muscle and connective tissue, is hard, swollen, and nodular.

CASE REPORT

Mrs. A. M., a 25-year-old, married, white woman, gravida ii, para ii, children 5 and 1½ years old, respectively, entered the Milwaukee County General Hospital on Feb. 2, 1939. She had been a patient in the hospital on two previous occasions, the first time in November, 1937, seven months after delivery of her youngest child, when

involvement of the genitalia with tuberculosis, since no other cause for the infection can be ascertained. The two most common complaints were pain in the lower abdomen confined to one or both sides, and vaginal discharge, usually of long standing. A record of the various other symptoms encountered, in their order of frequency, were weight loss, urinary distress, vomiting, weakness, cough, abdominal mass, fever and chills. We believe, however, that these symptoms offer little value from the standpoint of differential diagnosis, since they are often encountered in many other acute and chronic ailments involving the pelvis and abdomen.

Eight patients of this series are alive and well, including one on whom a right salpingo-oophorectomy was performed in 1930 when the patient was 27 years old. We were unable to contact four patients, and therefore have no information as regards their present condition. The remaining three are known to be dead; one patient aged 21, died three days following a bilateral salpingo-oophorectomy. Another, aged 25 years, also had a libateral salpingo-oophorectomy followed by a very stormy postoperative course and died approximately four months later. The third patient, a 25-year-old negress with advanced pulmonary tuberculosis, made an uneventful recovery following a bilateral salpingectomy and left oophorectomy, but died of pulmonary tuberculosis six years later.

A very high incidence of immediate postoperative complications was evident. The most distressful of these was draining sinuses from the incision, many fecal in character and of long standing. Eight patients developed sinuses which drained from approximately four months to four years. Six of the surgical incisions healed primarily. The average postoperative stay in the hospital was found to be 43.4 days.

Pelvic tuberculosis may result from one of the following modes of spread: (1) Contiguity, from the soft tissues adjoining the pelvis; (2) lymphogenous, usually from the abdominal cavity; (3) hematogenous, from some distant focus; (4) primary, with direct inoculation by coitus.

The tubes are most commonly involved in tuberculosis of the female genitalia. Glass and Cresci⁴ have reported an incidence of 85.5 per cent in their series of 36 cases of genital tuberculosis at the Long Island College Hospital from 1923 to 1937.

Ascending infection from some other portion of the genital tract rarely, if ever, occurs, the infection usually originating from a tuberculous peritonitis with involvement of the perisalpinx or the endosalpinx or both, or from some focus elsewhere in the body. The original focus may heal while the newly formed lesion continues to flourish. Authorities estimate that in fully one-half of the cases of tuberculosis of the tubes, involvement of the endometrium has occurred.

Stevenson and Wharton⁵ report tuberculous endometritis in approximately 85 per cent of a series of 402 cases of tuberculous salpingitis collected in forty-seven years at Johns Hopkins Pathology Laboratory.

The supposed high incidence of involvement of the endometrium in tuberculous salpingitis is very important, since in patients with genital tuberculosis, microscopic study of uterine curettings alone would yield a diagnosis in at least 50 per cent of the cases. However, curettement

The case of tuberculosis of the cervix presented here appears to be, from the evidence so far at hand, one of the rare instances of primary tuberculosis. No tuberculosis could be demonstrated elsewhere in this patient although a careful search was made for a focus of infection. We feel hesitant, however, about presenting this as a primary case without reservation, since there are several unexplained signs and symptoms which point to a possible focus of tuberculosis elsewhere in this patient.

1. Unexplained hemoptysis in November, 1937.
2. Twenty-pound weight loss in the six months prior to surgery which may have been due to the excessive vaginal bleeding.
3. The pelvic adhesions which may have been on a basis other than tuberculosis. Careful examination failed to reveal involvement of the tube, uterus, or ovary.
4. Increased sedimentation rate in October, 1939, eight months following surgery.

COMMENT

Marked differences of opinion exist as to the method of treatment of genital tuberculosis. Surgery is advocated by a majority of gynecologists, the treatment centering itself around two groups: Those advocating conservative surgical measures, and others who insist that more radical treatment is the method of choice, including subtotal hysterectomy and bilateral salpingectomy, but sparing the ovaries wherever possible. Jameson¹³ reports the mortality rate to be 10 per cent higher when conservative operations are performed, and states that the prognosis of untreated or only medically treated cases is grave. He feels further that, although those surgeons endeavoring to remove only diseased structures from the pelvis are following sound gynecologic procedure, they err in that it is impossible to determine the amount of tuberculous involvement of the various structures macroscopically. When the tubes are involved, the surgeon has no alternative but to perform a bilateral salpingectomy, since bilateral involvement is estimated in as high as 90 per cent of the cases.¹⁴ Some authorities insist that tuberculous involvement of the salpinges is always bilateral. Attempts to spare the uterus in these cases is also considered hazardous, since uterine tuberculosis is estimated to exist in well over 50 per cent of the cases revealing tuberculous salpingitis. One or both ovaries may be spared if they do not appear involved, but this should be done with great caution since involvement cannot be ascertained without the aid of the microscope.

King³ is convinced that surgery should not be performed in the face of an active pulmonary tuberculosis, since the pelvic involvement is not as serious, and surgery may tend only to aggravate the chest condition. He feels that the essential part of the treatment then becomes heliotherapy in a sanatorium and states that this cannot be overemphasized.

X-ray therapy, introduced by Bircher in 1908, has warm advocates¹⁵ and has been used by some with much more success than surgery. The x-ray advocates claim that there is no contraindication to its use and feel that while many will be greatly benefited from surgery, there is an initial operative mortality rate of 7 to 8 per cent, together with a very high incidence of post-operative complications.

SUMMARY

1. This report is based on a study of 15 patients with proved pelvic tuberculosis, operated upon and treated at the Milwaukee County General Hospital in the past eleven years.

she complained of intermittent radiating right lower abdominal pain which had occurred at intervals for five months. She also complained of menstrual irregularity for the past two months with almost daily bleeding for one month.

Three days prior to admission she began vomiting a greenish purulent material. On the day of admission she stated she had vomited about one-half cupful of blood.

Onset of menses occurred at 17 years, every twenty-eight days for three or four days. There was no menstrual disturbance up to the present illness. Family history was negative.

Examination revealed a well-preserved, 148-pound, white female, not acutely ill. General physical examination was negative except for slight tenderness over McBurney's point on deep palpation.

Vaginal examination revealed a freely movable cervix with third degree retrodisplacement of the uterus; no adnexal masses or tenderness were elicited. The cervix was lacerated and eroded. Laboratory findings were negative, as was the x-ray picture of the chest. The patient signed a release two days after admission.

One and one-half years after the first admission she was readmitted complaining of swelling and pain of five weeks' duration in the right inguinal region and right labia majora. Examination other than that performed by the interne was refused. This revealed a moderate white discharge and a right Bartholin abscess. The cervix appeared hypertrophied and eroded. There was a tender left adnexal mass, while the right side was negative. The right inguinal glands were markedly enlarged, tender, and warm. Cervical smears were positive for gram-negative intracellular diplococci. White blood count was 16,800, while other laboratory findings were negative. She again signed a release after a one-day stay in the hospital.

On her admission to the hospital in February, 1939, the patient complained of a chronic, foul-smelling, vaginal discharge present since shortly after the delivery of her youngest child one and one-half years before. She also complained of pain in the right lower abdomen for about one year. For five months she had suffered from a menorrhagia which had resolved itself into daily bleeding with a severe vaginal discharge two months later, requiring the use of two to three pads daily. She had lost approximately 20 pounds in the six months before this admission.

The positive findings on physical examination were mild tenderness on deep palpation in the right lower quadrant and some pelvic findings which revealed the uterus to be in third degree retrodisplacement. The size was not definitely determined but seemed larger and softer than normal. There was a large cystic, somewhat tender mass about 9 cm. in diameter in the right adnexa. The left adnexa were negative.

A diagnosis was made of (1) right cystic ovary, (2) third degree retrodisplacement of uterus, and (3) severe erosion of the cervix. Laboratory findings were negative.

A total hysterectomy and right salpingo-oophorectomy was performed under ether anesthesia by one of the authors. If tuberculosis of the cervix had been suspected, a more suitable anesthetic would have been used and a bilateral salpingo-oophorectomy performed.

The entire pelvis was filled with fine adhesions. The left tube and ovary were adherent to the posterior wall of the uterus, the right ovary being obliterated by a unilocular cyst measuring 10.5 cm. by 5 cm. in diameter. The sac was thin and filled with a gelatinous material.

Microscopic examination of the cervix revealed partial destruction of the surface epithelium, exposing the underlying cervical glands which were in some instances cystic in character. The stroma showed a marked inflammatory reaction, chronic in character, and in one area near the surface, tubercle-like structures with the characteristic cellular reaction of tuberculosis could be observed without caseous necrosis.

Sections through the endometrium, tubes, and ovaries showed no tuberculosis.

The patient was discharged in good condition on the tenth day after surgery. She was recalled to the hospital eight months later for re-examination. At this time she had no complaints and had gained three pounds in the past month. Pelvic findings were negative. Cystoscopic examination was negative, as was also a retrograde pyelogram. No tubercle bacilli could be demonstrated in either the gastric contents or the urine. The sedimentation rate was rapid; 29 mm. in one hour and 62 mm. in two hours. The chest x-ray picture was negative.

Since stilbestrol is two to three times as active as estrone¹ and seems to be equally as effective whether given by mouth or by injection,¹ it occurred to us that this drug might have a stimulating effect on endometrial regeneration. Theorizing further, it was felt that it might maintain a good uterine blood supply,^{11, 12} lend a better tone to the musculature by increasing the contractability,^{8, 9} sensitize the myometrium to oxytocics,⁸ and in this way bring about a greater resistance to puerperal infection and hasten involution.

After a preliminary trial with stilbestrol for three weeks, we found that 5 mg. doses could be tolerated with no apparent side effects; therefore, it was decided to administer the drug in this dosage to 200 consecutive operative obstetric cases, for it is in this group that the highest incidence of morbidity occurs. Our series began Jan. 19, 1940, and ended April 30, 1940, covering a period of the year in which our morbidity level is usually at its peak.

MATERIAL

Each operative case, excluding cesarean section, received 5 mg. of stilbestrol in oil intramuscularly within the first six to twelve hours following delivery and then received 5 mg. by mouth each morning until the day of discharge which was usually the tenth post-partum day. The average amount of stilbestrol received by each patient was 50 mg. This routine was carried out on 105 patients, after which time our supply of stilbestrol was exhausted. Ten days later the second series of cases was begun and for this group the dosage was changed. Each patient received 10 mg. of stilbestrol each day for the first three days and then 5 mg. a day for the remaining time in the hospital. During the first three days, one-half of the dose was given intramuscularly in oil. This procedure was carried out on 95 patients, making a total of 200 cases studied.

Thirty patients delivering spontaneously received diethylstilbestrol in 5 mg. doses daily, and in 23 of these attempts at endometrial biopsy were made, only one specimen being obtained from each patient. The time of biopsy varied from the eighth to the fourteenth post-partum day. The tissue for microscopic examination was removed with a biopsy forceps and curette. Because of the care which had to be used in such procedures, the specimens obtained were unsatisfactory in that they contained a large amount of cervical glands, endometrial stroma, and debris. None of the specimens showed amounts of endometrium sufficient to allow definite conclusions to be drawn. It was felt that further attempts at biopsy should be discontinued because of the added risk of infection and perforation of the uterus to the patient.

In the group of 200 cases studied, the following operative procedures were carried out at the time of delivery:

Episiotomy	194
Low forceps	189
Mid forceps	4
Breech extraction	5
Occiput posterior rotated with forceps	6
Occiput posterior rotated manually	2
Occiput transverse rotated with forceps	9
Occiput transverse rotated manually	6
Manual removal of placenta	2

Caudal block anesthesia was used in 178 of the 200 patients delivered. Gas-oxygen or gas-oxygen-ether was used in the remainder.

Our usual post-partum technique was carried out on all patients. Following delivery of the placenta, each patient received one ampoule of pitocin ($\frac{1}{2}$ c.c.) and if bleeding was excessive, ergonovine, ampoule 1, was given intravenously.

2. Significant facts brought out by this study are: (a) Generally all patients afflicted with genital tuberculosis fall into the "childbearing age" group with 80 per cent ranging between 20 and 30 years of age. (b) Pulmonary involvement was encountered in only 20 per cent of our cases. (c) Postoperative complications were high with an average postoperative hospital stay of 43.4 days. (d) Uterine tuberculosis was not encountered in any of our cases.

3. Differential diagnosis remains a major problem with 100 per cent incorrect preoperative diagnosis in our cases.

4. A case of cervical tuberculosis (probably primary) is presented.

REFERENCES

- (1) *Stevenson, Charles Summers*: AM. J. OBST. & GYNEC. 36: 1017, 1938. (2) *Finlaison, F. H.*: J. Obst. & Gynaec. Brit. Emp. 43: 473, 1936. (3) *King, James E.*: AM. J. OBST. & GYNEC. 35: 520, 1938. (4) *Glass, Morris, and Cresci, Joseph*: AM. J. Surg. 41: 216, 1938. (5) *Stevenson, Charles Summers, and Wharton, Laurence R.*: AM. J. OBST. & GYNEC. 37: 303, 1939. (6) *Bishop, Everett L.*: AM. J. OBST. & GYNEC. 19: 822, 1930. (7) *Danforth, William C.*: Ann. Surg. 106: 407, 1937. (8) *Schmitz, Herbert E., and Geiger, Clyde J.*: Illinois M. J. 75: 80, 1939. (9) *Fischer, Henry S., and Held, David*: AM. J. OBST. & GYNEC. 37: 339, 1939. (10) *Collins, Donald C.*: J. A. M. A. 112: 605, 1939. (11) *Lester, Charles W.*: Am. J. Surg. 33: 574, 1936. (12) *Douglass, Marion, and Redlon, Magnus*: Surg. Gynec. Obst. 48: 408, 1929. (13) *Jameson, Edwin M.*: AM. J. OBST. & GYNEC. 27: 173, 1934. (14) *Siddall, R. S.*: J. Michigan M. Soc. 35: 561, 1936. (15) *Lenz, Maurice, and Corscaden, James A.*: Am. J. Surg. 33: 518, 1936.

A CLINICAL STUDY OF THE EFFECTS OF DIETHYLSTILBESTROL ON PUERPERAL WOMEN

H. F. CONNALLY, JR., M.D., D. I. DANN, M.D., J. M. REESE, M.D., AND
L. H. DOUGLASS, M.D., BALTIMORE, MD.

(From the Obstetrical Service of the Baltimore City Hospitals)

SINCE the reports by Dodds,^{1,2} in 1938, diethylstilbestrol has been used experimentally by numerous workers and various results have been obtained and reported. Most of the literature deals with the estrogenic activity of this drug in relation to menopausal symptoms and cases of primary and secondary amenorrhea. To our knowledge stilbestrol has been administered to only a few post-partum patients and the reports made with reference to tolerance and the effect of this synthetic estrogen on lactation.³⁻⁵

Our experiment began with the idea of determining what effects, if any, diethylstilbestrol would exhibit on the puerperal uterus, since urinary estrogen levels are normally low following the third stage of labor;^{6,10} also to determine any alteration in the process of endometrial regeneration. In addition, we became interested in noting whether or not such changes would affect the incidence of puerperal endometritis.

In 1931 Williams, J. W.,⁷ studied a large number of puerperal uteri and was able to show "that from about the fourteenth day onward, the uterine cavity outside of the placental site is completely lined by epithelium although several more days elapse before the endometrium can be regarded as fully restored." He also stated that six to seven weeks appeared to be required for the disappearance of the placental site.

SUMMARY

Diethylstilbestrol was administered to 200 puerperal women in an attempt to show the effects of estrogens on the post-partum uterus with special reference to endometrial regeneration. Due to unforeseen difficulties, our primary objective could not be reached, but certain interesting clinical observations were noted and considered worthwhile reporting.

CONCLUSIONS

1. In this group of women no case under observation showed any single toxic side effect, even though the drug was pushed to more than the usual therapeutic dose.

2. From clinical observation only, these uteri sensitized by the drug apparently responded more readily to oxytocics than those in the control group.

3. Lactation was apparently suppressed in 70.5 per cent of the cases observed. However, in the dosage used complete inhibition was not noted, although the onset of lactation was delayed longer than in the control group. No incidence of engorged or painful breasts was noted in the treated group.

4. Clinically, the flow of lochia was not materially changed.

5. Stilbestrol apparently had no immediate effect on early involution of the puerperal uterus; however, pelvic examinations on about the twenty-first post-partum day revealed a more rapid involution than occurred in the control group.

6. Whatever the effects of stilbestrol on the parturient uterus may be, it was noted from the clinical standpoint that our morbidity in treated patients was materially affected, being 4 per cent as against a total morbidity of 12.8 per cent for the year 1939. Since our series included only operative cases, it would be supposed that the morbidity rate would be higher than the 12.8 per cent figure for 1939, which included normal as well as operative deliveries.

7. At this time we cannot advocate the routine use of diethylstilbestrol in the prophylactic therapy of puerperal endometritis; however, we hope that further investigations on this subject will be carried out.

Biopsy specimens were prepared and examined by the University of Maryland Department of Pathology.

The diethylstilbestrol used in this experiment was supplied by Abbott Laboratories.

REFERENCES

- (1) *Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.*: *Nature* 141: 247, 1938.
- (2) *Dodds, E. C., Lawson, W., and Noble, E. L.*: *Lancet* 1: 1389, 1938.
- (3) *DeLee, J. B., and Greenhill, J. P.*: *Year Book of Obstetrics and Gynecology*, p. 604, Ed. note, 1939.
- (4) *Winterton, W. R., and MacGregor, T. N.*: *Brit. M. J.* 1: 10, 1939.
- (5) *Kellar, R. J., and Sutherland, J. K.*: *J. Obst. & Gynaec. Brit. Emp.* 46: 1, 1939.
- (6) *Wolf, William*: *Endocrinology in Modern Practice* 1936, p. 580.
- (7) *Williams, John Whitridge*: *AM. J. OBST. & GYN.* 22: 664, 1931.
- (8) *Wolf, William*: *Endocrinology in Modern Practice*, 1936, p. 577.
- (9) *Falls, F. H., Lackner, J. E., and Krohn, L.*: *J. A. M. A.* 106: 271, 1936.
- (10) *Zondek, B.*: *Die Hormone des Ovariums und des Hypophysenvorderlappens*, Berlin, 1931, Julius Springer.
- (11) *Markee, J. E.*: *Am. J. Physiol.* 100: 32, 1932.
- (12) *Pompen, A. W. M.*: *De Invloed van Menformon op de Baarmoeder*, Thesis, Amsterdam, 1933.

*Obtained from *Reynolds, S.R.M.*: *Physiology of the Uterus*, 1939.

Routinely, each patient received 0.2 mg. of ergonovine by mouth every four hours for 6 doses. This was repeated in the majority of cases on the third post-partum day.

RESULTS

Toxic Effects of the Drug.—Of the 200 patients receiving stilbestrol, not a single side effect was noted that could be attributed to the drug. One patient developed a generalized urticarial rash on the seventh post-partum day, but this was most probably due to a barbiturate she received the night before, since she gave a history of previous attacks.

As already noted by Greenhill,³ puerperal women apparently have a "special tolerance to the drug." The fact that they were kept in bed may have influenced somewhat the toxic effects. However, if the toxic action of stilbestrol is central, we should have witnessed a higher incidence of toxic symptoms.

Sensitization of the Uterus to Oxytocics.—For the first four days post partum, it was observed that the uterus responded better than usual to oxytocics. This was purely a clinical observation and was not supported by experimental data.

Lactation.—Lactation was suppressed in 70.5 per cent, or 141, of the 200 cases reported here. With the dosage used we did not succeed in completely inhibiting lactation in a single incidence, although its onset was delayed to about the fifth or sixth day. It was interesting to note that none of the patients complained of engorged or otherwise painful breasts.

Lochia.—The flow of lochia did not seem to be changed in any way except that there was an increased flow in the seven cases of puerperal endometritis.

Post-partum Examination at Time of Discharge.—The vaginal mucosa was conspicuously pale and appeared to have shrunk somewhat as contrasted to the congested friable mucosa of the untreated cases. The cervix except for its mucosal surface showed no changes grossly. Of the 200 patients examined, 172, or 86 per cent, showed normally involuting uteri. Twenty-eight, or 14 per cent, of the patients showed enlargement of the uterus and were classified as subinvolved. Five of these patients returned within two weeks after discharge and showed well involuted uteri. No treatment had been advocated or followed in these cases.

Effects Observed Clinically on Morbidity.—The total number of patients having a temperature elevation to 100.4° F. or more at any time during the puerperium, excluding the first twenty-four hours immediately post-delivery, was 26, or 13 per cent, of the cases. The total number showing a single elevation to 100.4° F. or more was 16, or 8 per cent, of the cases. There were two cases or 1 per cent of the total that had two or more elevations to 100.4° F. or higher within a single twenty-four-hour period not classified as morbid.

For our morbidity standard, the first twenty-four hours post partum were excluded. After that, any patient who had two or more elevations to 100.4° F. or above on any two twenty-four-hour periods was classified as morbid. Temperatures were recorded every four hours.

On the basis of the above standard, 8 cases or 4 per cent of the 200 cases studied were morbid. One of these patients had pyelitis and 7 had puerperal endometritis. The corrected morbidity rate was 3.5 per cent. These figures are considerably lower than any obtained in this clinic previously. The total morbidity for 193 patients delivered by operative procedures between Oct. 1, 1939 and Dec. 31, 1939, receiving only the routine post-partum care, was 16.6 per cent. The total morbidity of the clinic during the same period last year, Jan. 1, 1939 to April 1, 1939, was 13.65 per cent, including all cases.

The results we obtained in our series affected the total morbidity of the clinic as follows: Total morbidity from Jan. 1, 1940 to April 1, 1940, 9.7 per cent. Operative morbidity during the same period, including 196 low forceps, 5 mid-forceps, and 21 breech extractions, 10.04 per cent.

To date, 20 per cent of the patients treated have been examined on or about the twenty-first post-partum day. In all cases the uterus was well involuted and approaching normal size. Lactation seemed to return in those patients who continued nursing their babies after the stilbestrol was discontinued. There were no complaints concerning the breasts. All patients reported a slight bloody discharge for one day to two weeks after leaving the hospital. This does not seem to vary from the usual post-partum course.

eighth, ninth, and tenth lunar months. Mothers are available for observations either once each day or once each week, and the fetal heart is recorded at each of these instances over one or more five-minute periods. We have accumulated, therefore, many thousands of minutes of heart records. The methods of recording have been described elsewhere.¹⁰ From this material we have selected all records taken under conditions of no known stimulation to either mother or fetus, to determine the frequency with which rates of 160 and above, and 120 and below, are to be found during these normal pregnancies before labor had begun. We have available 18,517 half-minute samples of such "normal" fetal heart rate. Eighty per cent of these were collected during the ninth and tenth months of pregnancy. To us it seems very doubtful whether fetal heart rates which occur normally during the ninth and tenth lunar months can be considered evidences of fetal distress during labor.

Table I shows the number of fetuses whose heart rate was 160 or above during one or more of the sampling periods. It also shows the total number and percentage of half-minute rates which were above this figure. The distribution of rapid rates varies tremendously. Rapid rates are sometimes maintained for a number of consecutive half-minute periods. In other instances the rate rises from 130 or 140 beats per minute to 170 or more and returns within a minute. Wide and rapid fluctuations without apparent cause other than bodily activity are common. Table II shows the same type of data for rates which dropped below 120. As indicated by the table, rates below 120 before labor are rare.

TABLE I. NUMBER AND PERCENTAGE OF FETUSES AND HEART RATE SAMPLES SHOWING RATES OF 160 AND ABOVE

MONTHS	TOTAL CASES	CASES WITH RATES 1 OR MORE TIMES ABOVE 160	%	TOTAL ½ MINUTE SAMPLES OF HEART RATE	NO. OF SAMPLES ABOVE 160	%
10	50	39	78	8963	539	6.2
9	46	33	72	5303	441	8.3
8	41	21	51	2787	136	4.9
7	22	10	45	991	91	9.1
6	10	7	70	484	84	17.3

TABLE II. NUMBER AND PERCENTAGE OF FETUSES AND HEART RATE SAMPLES SHOWING RATES BELOW 120

MONTHS	TOTAL CASES	CASES WITH RATES 1 OR MORE TIMES BELOW 120	%	TOTAL ½ MINUTE SAMPLES OF HEART RATE	NO. OF SAMPLES BELOW 120	%
10	50	14	28	8963	39	0.4
9	46	8	17	5303	23	0.4
8	41	4	10	2787	11	0.4
7	22	1	4	991	1	0.1
6	10	0	0	484	0	0

Fig. 1 shows the incidence of half-minute heart rates which exceed 160 beats per minute for all cases and all months of pregnancy. It gives no indication of the degree to which the 160 beat rate was exceeded, but shows the frequency with which excessive rates occurred in the group. This histogram indicates that for 81.2 per cent of the group some samples exceeding 160 would be expected in

NORMAL VARIATIONS OF FETAL HEART RATE DURING PREGNANCY

LESTER WARREN SONTAG, M.D., AND HELEN NEWBERY, M.A.,
YELLOW SPRINGS, OHIO

(From the Samuel S. Fels Research Institute, Antioch College)

OF THE limited number of criteria which are available for judging the state of well-being of the fetus during pregnancy and labor, the rate and variations of rate of the fetal heart are usually considered among the most important. There are two reasons for the stress laid upon fetal heart rate as an indicator of the condition of the fetus. Perhaps the first reason is that it is one of the few physiologic phenomena of the fetus which may be observed accurately and at will. Second is the fact that fetal distress in the form of anoxemia is widely believed to manifest itself earliest through a change in cardiac rate. We do not mean to imply that asphyxia is considered the only cause of abnormal deviation in heart rate. Leff¹ has advanced the theory that marked slowing of the fetal heart is the result of an overdistention of the fetal circulation from squeezing out of the blood from the placenta in prolonged labor.

There is not clear agreement as to what constitutes an abnormal heart rate.

The figure frequently found in American textbooks (Curtis,² Williams,³ etc.) is above 160 or below 100. Many authors consider that heart rates above or below these figures imply fetal distress and are usually an indication for operative interference. Bartholomew⁴ states that, while a rate of 160 or above is considered dangerous, he does not find it so. He believes, on the other hand, that a rate below 120 is a signal of distress, indicating asphyxia. Richardson⁵ considers that a fetal heart rate of 150 to 160 in ablatio placenta indicates one-fourth separation of the placenta and from 170 to 190, one-half separation of the placenta. Sachs⁶ fixes the normal range of fetal heart rate at from 132 to 144. He considers that figures below 100 and above 160 are not without physiologic "consequences." While he states that rates above 160 are abnormal they are not in themselves indication for forceps delivery. He believes that wide fluctuation indicates danger. Willibald⁷ believes that slow fetal heart rates during labor are more commonly due to pressure exerted on the head than to interference with fetal maternal gaseous interchange. Rech⁸ says that the fetal heart rate is not changed either by oxygen deficit or excess carbon dioxide in the fetal blood. Bartram⁹ concluded that it was impossible to determine the exact causes of changes in fetal heart rate during labor. In some of his cases, slowing of heart rate to 100 or below for an hour was harmless. In other cases, irregularities for a much shorter time were followed by death.

At the Samuel S. Fels Research Institute we have had under observation during the last half of pregnancy some 200 women. Of these, 63 have been available for repeated observations on fetal heart rate. We have, therefore, been able to accumulate from these 63 women a large amount of data on fetal heart rate during the sixth, seventh,

every 100 samples studied. For 46.9 per cent of the group five or more extreme samples would be expected in every 100, for 29.7 per cent of the group, 10 or more in every 100, and so on. Fig. 2 presents means, standard deviations and extremes for the total number of heart rate samples studied in each month of pregnancy. The extremes of our "normal" samples ranged all the way from 105 to 200 beats per minute. We found no instances where the rate dropped below 100 for a period of one-half minute or more. Short periods of very slow rate, lasting only a few seconds, occur not infrequently. They are of too short duration, however, to be apparent in a half-minute sample.

It should be emphasized here that all of these fetal heart rates were taken before the onset of labor. In those instances in which the rate has arisen above 160 or dropped below 120, there can be no question, therefore, of obstetric emergency, nor is there any reason to suspect anything abnormal about the selection of the cases. Mothers who volunteered for this study did so as a part of their participation in the general program of the Fels Research Institute and in no instance because of illness or suspicion of fetal abnormality. Heart rates which in this group have been found to be beyond what are commonly defined as normal limits have been beyond these limits without the existence of pathologic labor factors.

SUMMARY

The analysis of 18,517 half-minute samples of fetal heart rate on 63 normal fetuses ranging throughout the last five lunar months of pregnancy shows that rates of 160 or more beats per minute are common. Rates below 120 beats per minute are, on the other hand, unusual. Rates below 100 were not found in our group. Marked fluctuation in rate is frequently found.

CONCLUSIONS

Increase in fetal heart rate above 160 per minute occurs so frequently during the two months preceding labor that occurrence during labor seems little justification for assuming fetal distress. Marked fluctuations in rate are common during the last two months of pregnancy in normal fetuses. Since rates below 100 were not found in our group, it seems justifiable to conclude that low rates are as a rule the direct result of the effects of labor. High rates occur normally during the latter months of pregnancy and should be interpreted with caution when found during labor.

REFERENCES

- (1) *Leff, M.*: AM. J. OBST. & GYNEC. 24: 898, 1932.
- (2) *Curtis, A. H.*: Obstetrics and Gynecology, Vol. II, Philadelphia, 1933, W. B. Saunders Co., p. 80.
- (3) *Williams, J. W.*: Obstetrics, New York, London, 1924, D. Appleton & Co., p. 207.
- (4) *Bartholomew, R. A.*: AM. J. OBST. & GYNEC. 10: 89, 1925.
- (5) *Richardson, G. C.*: Ibid. 32: 429, 1936.
- (6) *Sachs, E.*: Ztschr. f. Geburtsh. u. Gynäk. 82: 284, 1920; Abst. J. A. M. A. 76: 417, 1921.
- (7) *Willibald, W.*: Ztschr. f. Geburtsh. u. Gynäk. 101: 724, 1932.
- (8) *Rech, W.*: Arch. f. Gynäk. 147: 82, 1931.
- (9) *Bartram, G.*: Ztschr. f. Geburtsh. u. Gynäk. 84: 33, 1921; Abst. J. A. M. A. 78: 554, 1922.
- (10) *Sontag, L. W., and Richards, T. W.*: Child Development Monographs 3: 7, 1938.

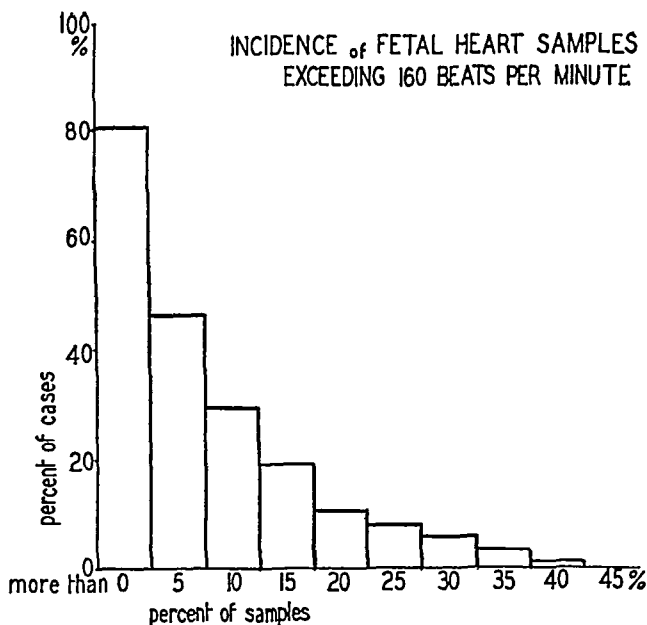


Fig. 1.—This histogram shows the incidence of half-minute heart rate samples in our 63 cases which exceeded 160 beats per minute any time during the last five lunar months of pregnancy.

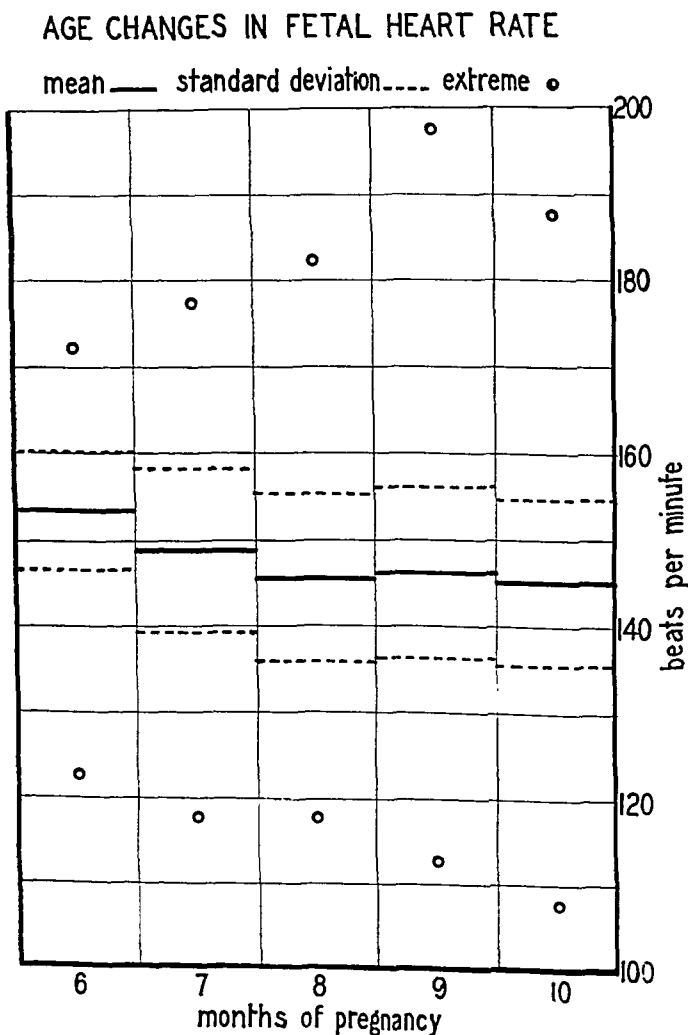


Fig. 2.—This diagram presents the means, standard deviations, and extremes for the total number of heart rate samples for each month of pregnancy. The extremes ranged from 105 to 200 beats per minute.

under direct vision, and blood-tinged amniotic fluid escaped. No analgesia was given other than the open drop ether, and after a strong labor of six and one-half hours, a spontaneous delivery occurred (March 17, 1938). The infant (male) weighed 3,070 Gm., did not require resuscitation, and appeared to be in good condition.

Three hours after birth bright bleeding was observed from the penis and mouth of the child and a bloody defecation took place. Petechiae were seen in the skin of the buttocks. The red cell count was 3,500,000, white cell count 41,500, and two nucleated red cells were counted per 100 white cells. The bleeding time was 60 minutes, and the clotting time was 10 minutes. The child was cyanotic at times. A transfusion of 60 c.c. of blood was given. The child died four hours later, or thirteen hours after birth. A blood culture was negative after five days of incubation, and the Wassermann reaction was 4-plus. Autopsy was permitted, and the positive findings included slight subarachnoid hemorrhage, petechiae and hemorrhages into the lungs, thymus, epicardium, myocardium, and scalp. No evidence of syphilis was found in the liver, and the epiphyseal line of the femur was normal. The placenta weighed 530 Gm., and careful inspection of the membranes and fetal surface failed to reveal vascular lesions that might produce the bloody amniotic fluid. On histologic section no evidence of syphilis was apparent. The death was attributed to hemorrhagic disease of the newborn.

CASE 2.—The mother, a 28-year-old, para 5-0-0-4, negro, had a 1-plus Wassermann reaction. She had stigmas of congenital syphilis, including eighth nerve deafness and Hutchinsonian teeth. She was given 2.25 Gm. of neoarsphenamine, 1.1 Gm. of arsphenamine, and 0.6 Gm. of bismuth during the antenatal course. A secondary anemia developed (the hemoglobin was 58 per cent, with a packed cell volume of 28 per cent), which responded to treatment. In addition a Type V pneumococcus lobar pneumonia developed in the seventh month of gestation for which 440,000 units of horse serum were administered. The weight remained stationary after the pneumonia, and there was no sign of toxemia of pregnancy. Labor occurred spontaneously in the forty-first week of gestation and continued without analgesia. The delivery (Feb. 13, 1939) was also spontaneous, after a hard type of labor with a total duration of only three hours and twenty-three minutes of which only eight minutes was spent in the second stage. At this time the membranes were observed to rupture with a gush of blood-stained fluid, more of which was noted immediately after the birth of the baby. The placenta weighed 750 Gm., and careful examination of the fetal surface and of the membranes failed to disclose any source for the blood in the amniotic fluid. Histologic section failed to reveal any evidence of syphilis.

The infant (female) weighed 3,780 Gm., and required simple resuscitation. Bleeding began three hours after birth, and was observed from the mouth and also as a copious bloody stool. The red cell count was 4,200,000, hemoglobin 69 per cent (16 Gm.), white cell count was 26,100, with 17 normoblasts per 100 white cells in the smear. The bleeding time was two and one-half minutes, and the clotting time was nine minutes. Three transfusions were given (total 155 c.c.) with cessation of the bleeding. The neonatal course was complicated by a mild gastrointestinal upset, but the infant was ultimately discharged as well. The Kline and Wassermann reactions were both negative on the infant's blood.

CASE 3.—The mother was a 22-year-old white primigravida, with a negative Wassermann reaction. Her antepartum course was complicated by slight vaginal bleeding in the twenty-seventh week of gestation. Examination at that time revealed a uterus of normal development, relaxed, and the cervix was tightly closed and presented a large erosion which bled easily, to which the bleeding was attributed. There was no evidence of toxemia. The pregnancy continued without further bleeding until the thirty-sixth week of gestation when labor began spontaneously. The patient was admitted to the hospital having very strong contractions lasting up to two minutes, the uterus relaxed poorly, and the cervix was almost fully dilated. A considerable bloody show was evident but was considered no more than ordinary. The patient delivered (May 14, 1939) soon after admission and after a total labor of five hours, no analgesia having been given. The meas-

INTRAUTERINE ONSET OF HEMORRHAGIC DISEASE OF THE NEWBORN

CARL T. JAVERT, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, New York Hospital and
Cornell University Medical College)*

HEMORRHAGIC disease of the newborn is generally believed to have its onset from the second to the sixth day of life, as shown by the reports of Diamond, Salomonsen, and others. In a recent paper,⁴ I stated that the clinical evidence of bleeding occurred on the first day in over one-third of my cases. This observation stimulated the conclusion that the disease runs part of its course in utero, and that antenatal and intranatal factors are contributory. I called attention to the higher incidence of antepartum complications of pregnancy, namely, anemia, toxemia, and treated syphilis, in the mothers of these infants. It was observed further that labor was often prolonged, or if short, that the uterine contractions were unusually strong. Each contraction of the uterus expresses blood from the placenta into both the arterial and venous portions of the fetal circulation; the patent ductus venosus, ductus arteriosus, and foramen ovale permit the increased pressure to be distributed to all parts of the body of the infant. This results in separation of the endothelial cells of the capillaries and probably explains the development of petechiae and ecchymoses in the internal organs and soft tissues in a varying degree. This may occur even after a normal labor. These hemorrhages may be regarded as physiologic and probably become pathologic when the coagulation mechanism is deranged. On the basis of this evidence I concluded that "abnormal clotting factors do not produce hemorrhages per se, but rather allow bleeding precipitated by the forces of labor to continue."

The development of bleeding from the fetus while still in utero was observed recently in three cases of hemorrhagic disease, two of which were associated with bloody amniotic fluid, and in the third case, intra-placental and retroplacental hematomas were observed. In each instance labor was short but severe, with long hard uterine contractions.

CASE 1.—This negro mother was a 37-year-old primigravida, with a 4-plus Wassermann discovered during pregnancy, for which she was given 3.3 Gm. of neoarsphenamine and 0.2 Gm. of bismuth during the antenatal course. A moderately severe pre-eclamptic toxemia developed, with rise in blood pressure to 165/110 mm. albuminuria, and a uric acid content of 10.8 mg. per 100 c.c. The patient did not respond to the usual measures, including intravenous glucose, and developed epigastric distress with nausea and vomiting. The weight during pregnancy had not increased appreciably. In the thirty-eighth week of gestation a medical induction of labor was done, with castor oil, quinine and nasal pituitrin, because of the toxemia. It was successful. The contractions became so severe that the nasal pituitrin was discontinued after the second dose. Ultimately open drop ether was necessary during contractions in order to secure proper relaxation of the uterus, although at no time was the fetal heart irregular. The membranes presented at the introitus when the cervix was 8 cm. dilated, and were ruptured artificially

disease. It seems plausible to consider the hematomas in the placenta as of fetal origin probably developing on the basis of low prothrombin concentration in the infant. While no prothrombin determinations were done on Cases 1 and 2, it may be possible that they were also very low, since the mothers of both infants had received antisyphilitic therapy which may have had an effect on prothrombin formation in these infants.

The recent work of Shettles and Hellman on the administration of synthetic vitamin K to mothers in the last month of pregnancy and during labor showed that the level in the infant could be raised 3 times the usual level. Waddell and Guerry have given it to the infant after delivery and have raised the prothrombin level. The prophylactic use of vitamin K therapy in mothers and their infants with prolonged labors, short severe labors, toxemia of pregnancy, treated syphilis, may lower the incidence of hemorrhagic disease, and (nontraumatic) intracranial hemorrhage.

CONCLUSION

Three cases of hemorrhagic disease which developed the first evidence of bleeding in utero were presented. Two patients had bloody amniotic fluid, and the third patient had intraplacental and retroplacental hematomas, with a prothrombin concentration of only 13 per cent of the adult normal, while the mother's concentration was normal. The low prothrombin concentration in the infants may be the precipitating factor in cases of premature separation of the placenta. The probable role of labor in producing hemorrhages and of a deranged clotting mechanism in permitting these to continue was mentioned. The reduction in prothrombin concentration in infants following maternal antisyphilitic therapy was postulated.

REFERENCES

- (1) *Brinkhous, K. M., Smith, H. P., and Warner, E. D.*: Am. J. M. Sc. 193: 475, 1937.
- (2) *Diamond, L. K., Blackfan, K. D., and Baty, J. M.*: J. Pediat. 1: 269, 1932.
- (3) *Hellman, L. M., and Shettles, L. B.*: Bull. Johns Hopkins Hosp. 65: 138, 1939.
- (4) *Javert, C. T.*: AM. J. OBST. & GYNEC. 35: 200, 1938.
- (5) *Javert, C. T., and Moore, R. A.*: Personal communication.
- (6) *Kugelmass, I. N.*: AM. J. OBST. & GYNEC. 38: 259, 1934.
- (7) *Quick, A. J., and Grossman, A. M.*: Proc. Soc. Exper. Biol. Med. 40: 647, 1939.
- (8) *Salomonsen, L.*: Acta Paediat. 27: Supp. I, 1939.
- (9) *Shettles, L., Delfs, E., and Hellman, L. M.*: Bull. Johns Hopkins Hosp. 65: 419, 1940.
- (10) *Waddell, W. W., and Guerry, DuP.*: J. A. M. A. 112: 2235, 1939.
- (11) *Warner, E. D., Brinkhous, K. M., and Smith, H. P.*: Am. J. Physiol. 114: 667, 1935.

ured blood loss in the third stage was 200 c.c. The placenta weighed 515 Gm. The maternal surface had six definite hematomas of varying depth and size, the largest measuring 5 by 2 by 2 cm. The margins of these showed definite organization and contained old tarry blood, and in others more recent clotted blood. On histologic section very definite hematomas were recognized.

The infant (male) weighed 1,980 Gm., and required resuscitation with carbon-dioxide-oxygen mixture. He had repeated cyanotic spells and soon began to bleed from the cord, nose, and mouth, and there was evidence of slight left facial paralysis. Death occurred four hours after birth, and just before transfusion was to be given. The Kline reaction was negative, the blood culture was negative, and spinal puncture yielded a slightly zanthrochromatic fluid which contained a few red cells. An autopsy was not permitted. Clinically, the cause of death was attributed to hemorrhagic disease and intracranial hemorrhage. Blood was taken at the time of delivery from the mother and from the cord blood of the placenta for prothrombin determinations. The mother had a packed cell volume of 31 per cent, and her prothrombin concentration was 83 per cent of normal; the infant had a packed cell volume of 49 per cent, and had a prothrombin level of 13 per cent of the adult normal. (Titration method of Warner, Brinkhous, and Smith was used.)*

DISCUSSION AND SUMMARY

In the 3 cases of hemorrhagic disease presented, clinical evidence of bleeding was apparent several hours after birth (first day of life). In each instance labor was severe and of short duration. The development of bleeding from the fetus while still in utero was evidenced by bloody amniotic fluid when the membranes ruptured in 2 cases, and by old and recent retroplacental hematomas in the third case. In the latter case the view is taken that these hemorrhages were probably of fetal rather than maternal origin, since the placenta is a fetal organ. These findings support the original observations of the author regarding the intrauterine course of hemorrhagic disease and suggest that the bleeding is probably precipitated by the forces of labor. Such physiologic bleeding becomes pathologic and continues because of a deranged clotting mechanism. This point receives further substantiation by a review of over 700 infants delivered by cesarean section in this Clinic; only one child so delivered had the disease, and it had experienced a labor of sixty hours before delivery. However, the case reported recently by Brinkhous, Smith and Warner had been delivered by cesarean section, which at first seems to discount this finding, but their patient also had a severe toxemia for which reason the cesarean section was performed.

The prothrombin concentration in the newborn infant has been studied by many investigators including Quick and Grossman, Brinkhous, Smith and Warner, Shettles, Delfs and Hellman, Kugelmass, Waddell and Guerry. Javert and Moore have had the opportunity of recording blood plasma prothrombin determinations in 20 parturient women at term and in the cord blood of their infants. The average concentration was 23 per cent, using the method of Warner, Brinkhous, and Smith, which is in agreement with 26 per cent obtained by Brinkhous, Smith and Warner. The low concentration of 13 per cent or half of the normal newborn level in Case 3 seems doubly significant since the child developed retroplacental hemorrhages as well as hemorrhagic

*These determinations were made possible through the courtesy of Dr. William DeWitt Andrus under a grant from the John and Mary R. Markle Foundation.

EXPERIMENTAL WORK AND DISCUSSION

Four cases are presented, one of which was studied for over three months. All patients were multiparas having a history of either failing or no milk supply with previous babies. In the first three cases the patients were allowed the regular hospital ration. In addition 1 Gm. each of cystine, glycine and glutamic acid was given with breakfast, 2 Gm. of each of the amino acids with dinner, and 2 Gm. with supper, making a total of 5 Gm. each per day. This combination of amino acids was used in order to allow the body material to manufacture glutathione. The suggestion came from the work of Daggs and Tomboulion.¹¹ It is not advisable to give too large a dose of cystine for fear of damaging the kidney (Curtis and others¹⁸). A diet high in the B vitamins, however, protects against this damage to a great extent (Hartwell¹⁹). None of these cases showed any sign of kidney disturbance even though one of the subjects had a moderate albuminuria before delivery. The amino acids were either sprinkled on the food or given in lemonade. All patients were cooperative and in favor of the experiment. The milk production was obtained by weighing the baby before and after nursing. Nursing was followed by pumping the breasts in the third case. Observations were made until the time of leaving the hospital. No means were available in these three cases for collecting data after that time. The results of the first three cases are shown in Fig. 1.

The patient in Case 1 showed no signs of milk secretion until the eleventh day. Just before leaving the hospital an additional 28 Gm. were obtained by breast pump (shown by the shaded area in the chart).

The patient in Case 2 was seen on the evening of the sixth day post partum, having shown no milk secretion. The amino acid feeding was started at breakfast the next morning. At 2 o'clock that afternoon 50 Gm. of milk were obtained by the infant from the breast. The following day the patient complained of engorged breasts. It might be argued that the milk was slow in starting to be secreted and would have started on the seventh day regardless of the feeding regime. This seems improbable since milk secretion generally begins before this time and the patient had a history of a lack of milk secretion with the previous baby.

Case 3 is particularly interesting since it was obtained sooner, second day post partum. The history revealed the following: Baby born three years before. Put to breast continuously for three months without obtaining any milk. Baby had to be given full formula from the third day on. . . . In this instance both the amount obtained by the baby and that by pump are recorded. It might be said that the application of the breast pump had a great deal to do with the milk flow, but a strong healthy baby was unable to obtain any milk during the previous confinement. Because of the many factors that may have influenced the results of the first three cases and because of the short periods of observation, it was decided that a longer more critical study of the next case should be made.

Case 4 was a multipara free from any metabolic or pathologic disturbance. She had had two children. The first child had been conscientiously put to the breast for a month but obtained very little milk and had to be given full formula at every feeding. The second child, born two years later, also was unable to obtain more than a small amount of colostrum. Three and one-half years later the third child was born. The growth of the baby, the milk production, and the amounts of cystine fed are shown in Fig. 2. Only a small amount of colostrum was obtained by the baby, and formula was given the first few days as indicated on the chart by the letter *F*. On the seventh day, when it seemed apparent that the milk production probably would be slight, 2 Gm. of cystine were given. From then

THE EFFECT OF CYSTINE ON HUMAN MILK PRODUCTION

R. G. DAGGS, PH.D., BURLINGTON, VT.

(From the Department of Physiology, College of Medicine, University of Vermont)

THE effect of diet upon milk production has constituted a matter of interest to many investigators.

Ssubotin,¹ in 1886, working with dogs found that the diet had an important effect upon the composition of the milk. Voit,² in 1869, showed that a high protein diet was particularly effective in stimulating milk production. Hoobler³ studied the effect of various forms and quantities of protein upon human milk production. His work brought out the importance of a diet relatively high in good quality animal protein. The findings of Adair,⁴ using a large series of human subjects, further emphasized the advisability of a high protein diet. Hitchcock⁵ has shown that rats raised larger and healthier litters when they were fed meat in addition to an adequate balanced diet. Daggs,⁶ working with dogs, showed liver to be the best source of protein of those tried.

The conclusions were borne out not only by the quantity of milk produced but by the quality as well. The nitrogen retention in the mother was better and the growth of the pups superior for those animals receiving the liver diet.

The next step was to find what factor in the liver was acting as the lactagogue.

Wilkinson and Nelson⁷ claimed fresh liver contained a lactation-promoting substance that was destroyed at 120° C. and was not soluble in ether. Smith and Seegers⁸ found an alcohol and water soluble, ether insoluble substance in liver capable of stimulating lactation in rats. Mapson⁹ demonstrated the presence of a lactagogue which he called "physin" in a water extract of autolyzed liver. Nakahara and his associates,¹⁰ in a series of papers, show evidence for the existence of a lactation vitamin (L₁) that may be obtained from beef liver. Daggs and Tombouljian¹¹ demonstrated that protein degradation products, extracts and amino acids that contained the lactation principle all had a relatively high sulphur content. Daggs and Lidfeldt¹² showed that cystine, cysteine, and methionine acted as lactagogues. Wright and Haag¹³ presented evidence that the lactation-promoting properties of rations containing alfalfa proteins were markedly enhanced by the addition of cystine. In another paper,¹⁴ they postulated the belief that cystine and methionine serve to make sulphur-deficient protein nutritionally complete rather than to act as lactation stimulants per se. It is our belief that the S-H-containing amino acids do more than this. Daggs and Tombouljian¹¹ pointed out that, "It is definitely known that casein is relatively low in cystine and it may be surmised that the added cystine is merely making a more complete protein of casein. But liver and egg are both considered sources of good complete proteins, and even when fed at practically two times the level they did not give as good results as the casein plus cystine diet." The S-H compounds evidently are utilized in the secretion of milk as Harding and Cary¹⁵ suggested. Whether they act directly upon the mammary gland cells or through the pituitary we cannot say as yet. Recent work concerning the action of glutathione on cellular proliferation would tend to support the former view. The fact that prolactin contains sulphur (White and others¹⁶) may suggest the idea that cystine is needed by the pituitary to produce prolactin. However, the hormone prolactin does not have the same marked effect upon human beings that it does on pigeons. Ross¹⁷ has shown that it takes very large doses of prolactin to increase milk production even to a slight extent in human beings.

had no effect on the fat, protein, or ash content of the milk. On the eighty-sixth day, tetany and engorged breasts were produced by increasing the cystine fed. The condition again was relieved by using the breast pump. Cystine administration was then stopped and the breasts were practically dry two weeks later.

TABLE I. MILK ANALYSIS—CASE 4

DAYS POST PARTUM	VOLUME C.C.	FAT %	LACTOSE %	PROTEIN %	CYSTINE FED GM.
80	490	2.8	7.2	1.07	0
81	450	3.8	6.8	0.98	2
82	—	—	—	—	2
83	—	—	—	—	1
84	425	3.6	—	—	1
85	—	—	—	—	1
86	505	4.9	6.5	1.20	0
87	465	4.3	6.7	—	0
88	525	4.2	6.9	—	0
89	490	—	—	—	0
98	250	2.2	7.0	1.10	0

COMMENT

All patients showed a response to cystine feeding. Perhaps a much greater response could have been obtained with a combination of endocrine and dietary therapy. However, it is significant to note that whatever the endocrine set-up might have been, the diet therapy had some effect. It is undoubtedly true that the flow of milk is controlled to a great extent by heredity, a sort of individual hormonal pattern relationship. Conditions may be such that the mammary glands do not secrete the maximum amount which is fairly definitely set by heredity. It is this relatively large group of cases that we believe can be helped by dietary therapy. Diet plays a very important role in stimulating the gland to its maximum function. The sulphydryl containing amino acids are the particular dietary elements responsible for this stimulation.

SUMMARY

Multiparas having a history of lack of mammary function were given cystine by mouth. Milk secretion was stimulated in all cases. The analysis of the milk in one case showed an increased fat content following cystine feeding.

REFERENCES

- (1) *Ssubotin*: Virchows Arch. f. path. Anat. 36: 561, 1866.
- (2) *Voit*, C.: Ztschr. f. Biol. 79: 136, 1869.
- (3) *Hoobler*, B. R.: Am. J. Dis. Child. 14: 105, 1917.
- (4) *Adair*, F. L.: AM. J. OBST. & GYN. 9: 1, 1925.
- (5) *Hitchcock*, F. A.: Am. J. Physiol. 79: 218, 1926.
- (6) *Daggs*, R. G.: J. Nutrition 4: 443, 1931.
- (7) *Wilkinson*, P. D., and *Nelson*, V. E.: Am. J. Physiol. 96: 139, 1931.
- (8) *Smith*, H. G., and *Seegers*, W. H.: J. Nutrition 7: 195 and 209, 1934.
- (9) *Mapson*, L. W.: Biochem. J. 26: 970, 1932.
- (10) *Nakahara*, W., *Inukai*, F., and *Ugami*, S.: Science 87: 372, 1938.
- (11) *Daggs*, R. G., and *Tomboulis*, R. L.: J. Nutrition 9: 581, 1935.
- (12) *Daggs*, R. G., and *Lidfeldt*, V. S. M.: Ibid. 15: 211, 1938.
- (13) *Wright*, L. D., and *Haag*, J. R.: Ibid. 17: 263, 1939.
- (14) *Haag*, J. R., and *Wright*, L. D.: Ibid. 19: 563, 1940.
- (15) *Harding*, T. S., and *Cary*, C. A.: Proc. Soc. Exper. Biol. & Med. 23: 319, 1925-26.
- (16) *White*, A., *Catchpole*, H. R., and *Long*, C. N. S.: Science 86: 82, 1937.
- (17) *Ross*, J. R.: Endocrinology 22: 429, 1938.
- (18) *Curtis*, A. C., *Newburgh*, L. H., and *Thomas*, F. H.: Arch. Int. Med. 39: 817, 1927.
- (19) *Hartwell*, G. A.: Biochem. J. 22: 1212, 1928.
- (20) *Pertman*, I., *Stillman*, N., and *Chaikoff*, I. L.: J. Biol. Chem. 133: 651, 1940.

on to the eightieth day when the milk was taken for analysis, the infant received sufficient milk from the breasts to maintain a normal growth rate. On the twelfth day, two days after leaving the hospital, the patient developed a tetany and engorged breasts which were relieved by using the breast pump. The tetany probably was caused by the sudden shift of calcium from the body tissues to the milk. The milk production continued normal without cystine feeding until the thirty-eighth day when the baby appeared hungry and its weight curve began to flatten. On the thirty-ninth day, cystine again was given as shown on the chart. The patient learned to adjust the cystine dose so as to maintain normally filled

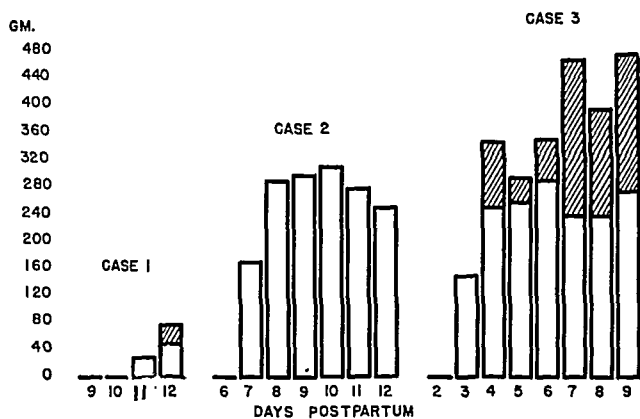


Fig. 1.

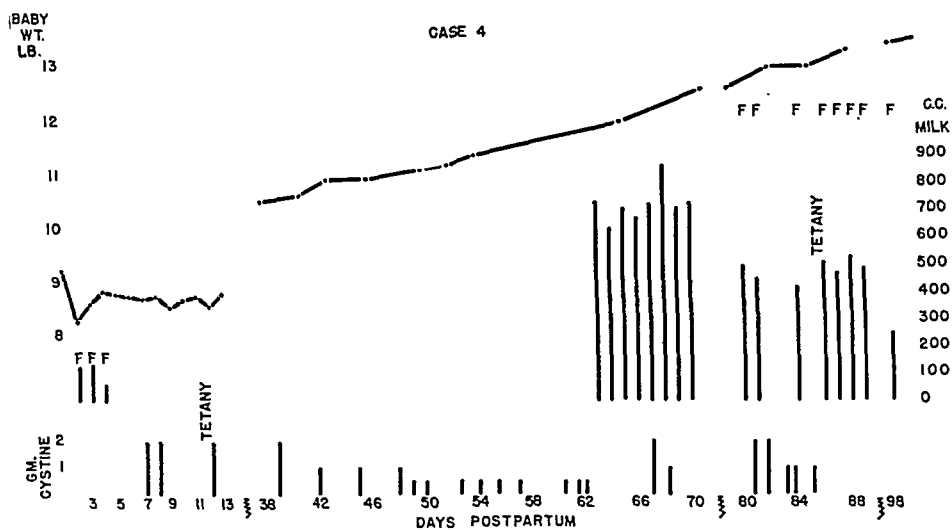


Fig. 2.

breasts. From the sixty-third to the seventieth day, the breasts were pumped, the milk measured, and then given to the baby by bottle. This procedure provided quantitative milk production data as shown in Fig. 2. The infant began taking cereal on the sixty-third day. The baby was put back to the breast from the seventy-first day to the eightieth day when the milk again was obtained by pump and analyzed for fat, carbohydrate, and protein. The results are shown in Table I. Note the increase in fat following the cystine feeding. Perlman, Stillman and Chaikoff²⁰ have recently shown that methionine, cystine, and cysteine accelerate the phospholipid turnover in the liver. This may be an explanation for the high fat content of the milk when cystine is fed. According to Ross,¹⁷ this change in composition of the milk does not occur with prolactin administration to human beings. Prolactin

c.c. were used to collect the placental blood. In one, 21.4 c.c. of the I. H. T.* solution recommended by Goodall and his co-workers⁴ was added to an equal quantity of blood. The anticoagulant was made up according to the formula of Bagdassarov¹ and consisted of sodium chloride, 7.0 Gm.; sodium citrate, 5.0 Gm.; potassium chloride, 0.2 Gm.; and magnesium sulphate, 0.004 Gm. in one liter of distilled water. In the other, 4.2 c.c. of a 3.5 per cent sodium citrate solution was added to 38.6 c.c. of blood to fill the container.

At the time of collection, a 5 c.c. portion was secured in an heparinized hematocrit tube. This served for the initial determination; its analysis revealed:

Hematocrit	{58.6% cells
	{41.4% plasma
Plasma specific gravity	1.0264
Total plasma proteins	6.63 Gm. %
Plasma potassium	23.7 mg. %
Whole blood potassium	227.0 mg. %
Cell potassium (calculated)	370.0 mg. %

After collection, the blood was stored in an electric refrigerator at 4° C. Samples were removed and tested with the results as tabulated in Table II.

TABLE II. COMPARISON OF OUTWARD DIFFUSION OF POTASSIUM IN PLACENTAL BLOOD STORED IN DIFFERENT PRESERVATIVES AT 4° C.

DATE	DAY OF STORAGE	MILLIGRAMS OF POTASSIUM IN PLASMA OF 100 C.C. OF BLOOD	
		I. H. T. SOLUTION	SODIUM CITRATE
8/17/39	0	9.8	9.8
8/19/39	2	33.4	32.5
8/26/39	9	68.9	55.9
9/ 2/39	16	88.6	57.1
9/ 9/39	23	107.5	77.2
Details of the experiment:			
Volume of cells		12.54	22.60
Volume of preservative		21.40	4.20
Volume of plasma		8.86	16.00
Total		42.80 c.c.	42.80 c.c.
Internal cylinder diameter: 1.8 cm.			

DISCUSSION

These findings indicate that the cell volume is approximately 22 per cent higher in placental blood than in that of the adult male; 37 per cent higher than in that of the adult female, and from 50 to 60 per cent higher than that of the reported average⁵ for mothers at term.

The specific gravity of the plasma and plasma proteins are approximately 10 per cent lower than the values found in normal adults.

The cell potassium is within normal limits, the whole blood values 25 per cent higher, and the plasma values 41 per cent higher than those found in adults.

CONCLUSIONS

1. The cell volume of placental blood is approximately 50 per cent higher than that of the mother, and 22 per cent higher than that of a normal adult male.

*Central Institute of Hematology and Transfusions of Moscow.

STUDIES ON THE PRESERVATION OF PLACENTAL BLOOD*

JOHN SCUDDER, M.D., CHARLES R. DREW, M.D., AND
VIRGIL G. DAMON, M.D., NEW YORK, N. Y.

(From the Surgical Pathology Laboratory of the College of Physicians and Surgeons,
Columbia University, and the Sloane Hospital for Women)

THE first reference to the use of placental blood for transfusions is found in an article by Rubin⁷ which appeared in 1914. Later, reports of its successful use were published by Malinovsky and co-workers⁶ in 1934, Bruskin and Farberova³ in 1936, and Stavskaya¹¹ in 1937.

The present rather widespread use and investigation of the method followed the report of Goodall, Anderson, Altimas, and MacPhail⁴ in 1938.

The purpose of this present investigation is threefold: to ascertain again what are some of the normal constituents of placental blood, to determine whether there is a loss of intracellular potassium, and to compare the Russian preservative with the accepted sodium citrate solution.

METHODS

Potassium was analyzed by the modified argenticobaltinitrite procedure.^{8, 12} Cell volume was determined by the hematocrit.⁸ The specific gravity of plasma was measured by the falling drop technique of Barbour and Hamilton,² from which data the total plasma protein concentration was calculated.¹³ The normal values are presented in Table I.

TABLE I. NORMAL VALUES FOR PLACENTAL BLOOD

NUMBER	CELL VOLUME IN PER CENT	PLASMA SPECIFIC GRAVITY	PROTEINS GRAMS PER CENT	MILLIGRAMS PER CENT		
				PLASMA POTASSIUM	WHOLE BLOOD POTASSIUM	CELL POTASSIUM
1	53.9	1.0250	6.16	22.5	235	417
2	68.0	1.0261	6.53	21.3	279	400
3	66.0	1.0280	7.18	27.2	279	409
4	51.9	1.0250	6.16	26.4	225	408
5	50.1	1.0250	6.16	21.3	242	460
6	48.4	1.0231	5.51	26.2	208	401
7	51.5	1.0276	7.04	19.1	211	392
8	58.6	1.0264	6.63	23.7	227	370
Average	56.1	1.0258	6.42	23.5	238	407

In the first six experiments done in 1938, placental blood was mixed with various preservatives and tested. The plasma potassium ranged from 45 to 214 mg. per cent at the end of forty days. No conclusions could be made from this series.

Subsequently, the shape of the flask, the concentration of carbon dioxide, agitation, and hydrogen ion concentration, as well as the selection of the preservative, came to be appreciated as a few of the factors limiting potassium diffusion.⁸⁻¹⁰

With this added knowledge, a controlled experiment was carried out. Two identically shaped cylinders, with ground glass stoppers, capable of holding 42.8

*This study was made possible by a grant from the Blood Transfusion Betterment Association, New York.

for any particular reason, but were taken consecutively. The restriction in diet was accomplished by having the patient desist from cooking her food with salt and from seasoning the food with salt at the table.

The results seemed to be so striking that it was felt that these should not suffer from the lack of an adequate control. Therefore, these results were compared with a similarly sized consecutive series of private patients (I. D.) of about the same social and economic class, and delivering during approximately the same period. And further the same changes in dietary regimen of pregnancy were then commenced in the private patients of the other author. All of the patients were delivered in the same hospital; and the hospital records were used in computing the duration of labor. Any personal interest in the results were thus removed since the computations were made from figures obtained by internes or residents (who were not aware of any study being in progress) in their histories; the same internes were involved since the patients delivered during the same period, thus removing any possible differences due to interpretation of the answers to the question "When

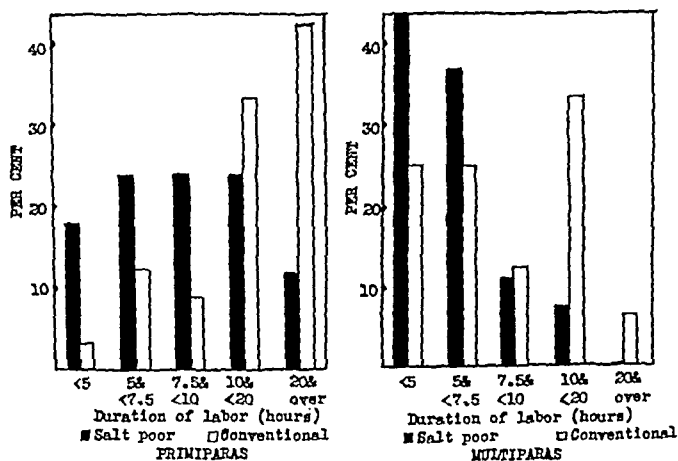


Fig. 1.

did your labor begin?" This is a question often difficult to decide since so many of us find difficulty in deciding "what is labor." If any error existed as to the decision when it actually began, it was approximately the same for all the cases involved. Likewise, because of the difficulty of deciding the end of the first stage of labor, the total duration of labor was taken for comparison, although it was fully realized that the effect of a salt poor diet would *probably* be on the first stage only.

RESULTS

There were 46 patients in the original group of patients on a salt poor diet, including 29 primiparas and 17 multiparas. The average lengths of labor were 9.6 hours and 6.5 hours, respectively. In the control series there were 49 patients, 33 primiparas and 16 multiparas; the average lengths of labor were 22.9 hours and 9.0 hours, respectively. In the second group (I. D.) on a salt poor diet, there were 32 patients, 22 primiparas with an average labor of 10.4 hours, and 10 multiparas with an average length of labor of 4.7 hours. If we add both salt poor

2. The total proteins are less in placental blood than in normal adult blood.

3. The increase in concentration of plasma potassium ion is reconfirmed.

4. The rate of potassium diffusion from the placental blood cells is of the same order as adult blood.

5. These potassium diffusion studies indicate that a final concentration of 0.35 Gm. per cent sodium citrate in preserved blood is a superior preservative to the more complex Moscow I. H. T. solution.

REFERENCES

- (1) *Bagdassarov, A.*: Sang 11: 466, 1937. (2) *Barbour, H. G., and Hamilton, W. F.*: J. Biol. Chem. 69: 625, 1926. (3) *Bruskin, Y. M., and Farberova, P. S.*: Sovet. vrach. zhur. 20: 1546, 1936; abst. J. A. M. A. 107: 2098, 1936. (4) *Goodall, J. R., Anderson, F. O., Altimas, G. T., and MacPhail, F. L.*: Surg. Gynec. Obst. 66: 176, 1938. (5) *Goodall, J. R., and Gottlieb, R.*: Canad. M. A. J. 35: 50, 1936. (6) *Malinovsky, M. S., Smirnova, L. G., Bayavshinova, M. S., and Tarzanova, V. G.*: Sovet. khir. 7: 179, 1934. (7) *Rubin, G.*: New York M. J. 100: 421, 1914. (8) *Scudder, J.*: Shock: Blood Studies as a Guide to Therapy. Philadelphia, 1940, J. B. Lippincott Company. (9) *Scudder, J., Drew, C. R., Corcoran, D. R., and Bull, D. C.*: J. A. M. A. 112: 2263, 1939. (10) *Smith, M. E., Tuthill, E., Drew, C. R., and Scudder, J.*: J. Biol. Chem. 133: 499, 1940. (11) *Stavskaya, E.*: Novy khir. arkhiv. 37: 72, 1937; abst. J. A. M. A. 108: 1226, 1937. (12) *Truszkowski, R., and Zwemer, R. L.*: Biochem. J. 31: 229, 1937. (13) *Weech, A. A., Reeves, E. B., and Goettsch, E.*: J. Biol. Chem. 113: 167, 1936.

THE EFFECT OF A SALT POOR DIET DURING PREGNANCY UPON THE DURATION OF LABOR

WILLIAM POMERANCE, M.D., AND ISIDORE DAICHMAN, M.D., F.A.C.S.,
BROOKLYN, N. Y.

EVER since the importance of a salt poor diet during pregnancy as a means of reducing the incidence of toxemias of pregnancy, especially eclampsia, was demonstrated, various reports¹⁻⁵ have appeared in the foreign literature concerning the effect of such a diet upon the duration of labor. Most reports evidenced a definite reduction in the duration of labor when such a restriction in diet was enforced in the last weeks of pregnancy. It was following one such report that one of us (W. P.) decided to place his private patients on such a regime.

While the reports in the literature concerned themselves with salt restriction in the latter weeks of pregnancy, it was decided to encourage the restriction of salt in the diet of these pregnant patients soon after the disappearance of the nausea and vomiting of the early months of pregnancy. This was done because of the difficulty in having ambulant patients do away with an element of their diet to which they were thoroughly habituated; it was thus felt that certainly during the latter two months of pregnancy the patient would have learned to accept such a salt poor diet. Likewise the testing was limited to private patients since many ward patients do not present themselves for prenatal care until late in pregnancy, and because less control can be exerted over such clinic patients than over private patients. The patients were not chosen

any other mechanism that may be thought of, is not known. Without some definite experimental proof of any of the above, it would be an idle effort to choose one over the other.

As to the possibility of any contraindications to such a diet, Hammarsten⁶ states that "man needs very little mineral matter and this in general is to be obtained from the daily food, since the latter contains a greater quantity than is required by the human body." The sole exception would seem to be sodium, which is necessary to the diet of people living almost exclusively on vegetables (especially potatoes, etc.) rich in potassium, which has a tendency to drive sodium out of the body. This would seem to be of not such great importance during pregnancy when there is a tendency to retain sodium in the body. The universal use of salt as a condiment by all classes, unconsciously leads to the habit of using it in excess of normal requirements which are variously stated as from 2 to 4 Gm. daily.⁷ According to Fitch,⁸ sodium and chloride equilibrium can apparently be maintained on less than one-fourth the amount of salt ordinarily consumed. Many of the ordinarily consumed foods are high in sodium: bread, butter, milk, cheese, egg white, lima beans, carrots, olives, raisins, spinach, wheat bran, clams, oysters, and meat.⁹ These are some of the staples of the diets of our community, and a marked inroad in the consumption of many of these would be necessary before the total requirements of the body would be interfered with.

CONCLUSION

It would seem quite evident, from a study of 78 cases on a salt poor diet and adequately controlled, that there is a definite reduction in the duration of labor following the use of such a diet during pregnancy.

NOTE: Since the preparation for publication of these results was begun, a paper appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY for May, 1940, on the same subject by Ernest E. Wadlow with essentially similar results.

REFERENCES

- (1) *Reeb, M., and Israel, L.*: Gynec. et obst. 27: 193, 1933. (2) *Israel, L.*: Gaz. d. hôp. 106: 591, 1933. (3) *Lambert, G.*: Zentralbl. f. Gynäk. 59: 2598, 1935. (4) *Karpati, J.*: Ibid. 59: 2601, 1935. (5) *Reeb, M.*: Gynec. et obst. 38: 321, 1938. (6) *Hammarsten, O.*: A Textbook of Physiological Chemistry, New York, 1912, John Wiley & Sons, Inc., p. 843. (7) *Bridges, M. A.*: Dietetics for the Clinician, Philadelphia, 1937, Lea & Febiger, p. 85. (8) *Fitch, W. E.*: Dietotherapy, New York, 1922, D. Appleton-Century Co., 2: p. 348. (9) *Bridges, M. A.*: Dietetics for the Clinician, Philadelphia, 1937, Lea & Febiger, p. 103.

140 EIGHTH AVENUE.

Kronfeld, Rudolf: Ovarian Dermoid Containing Teeth, J. Dent. Research 19: 145, 1940.

Teeth in ovarian dermoid cysts are not particularly rare but in contrast to Japanese, and especially German medical literature, but little has been published on this problem in this country. In a brief review of foreign literature the writer points to the fact that in any ovarian cyst, if they can be identified as right or left teeth, all of them always belong only to one side of the body.

In the case reported here the dermoid contained three erupted teeth and one tooth germ, outside of bone, hyaline cartilage, nervous and brain tissue, cysts, pigment cells, fat tissue, and skin with hairs, and sebaceous and sweat glands.

HUGO EHRENFEST.

groups together, we have 78 cases: 51 primiparas with an average length of labor of 9.9 hours and 27 multiparas with an average length of labor of 5.8 hours. These results are tabulated in Table I.

TABLE I

	PRIMIPARAS		MULTIPARAS	
	NO.	HOURS-LABOR	NO.	HOURS-LABOR
Salt poor Group I	29	9.6	17	6.5
Salt poor Group II	22	10.4	10	4.7
Salt poor Total	51	9.9	27	5.8
Conventional Diet	33	22.9	16	9.0

These results are better demonstrated graphically and when broken up as in Fig. 1.

From these it can be seen that two-thirds of the primiparas on salt poor diets delivered in less than ten hours, while only one-fourth on conventional diets did likewise. And similarly over four-fifths of the multiparas on salt poor diets delivered in less than 7.5 hours as compared with one-half on conventional diets who did the same.

DISCUSSION

Many factors, ranging from the psychic state of the individual to the size and shape of the pelvis, are determinants of the duration of labor in any case. It was for this reason that the limitations described above were placed upon the study made; it was felt that only in this way could many of these factors involved be approximately the same for the two series compared. No effort was made to determine either the degree of cooperation of the patients (the importance of the diet was stressed at almost each prenatal visit subsequent to the starting of the restriction) or the correlation of such cooperation with the duration of labor. Similarly, it was felt that possibly some of the patients on conventional diets had a relatively salt poor diet as a personal custom.

The foreign reports on this subject also speak of the reduction of the intensity of the labor pains as a result of the salt poor diet. No attempt was made to evaluate this point since it appeared to us that such an evaluation was fraught with the possibility of great error, there being no point of comparison for each patient. It would seem almost a priori that a patient having ten hours of pain would describe her pain as being less intense than one having twenty hours of pain of a similar character. Likewise no attempt is made to suggest a reason for this phenomenon of reduction of duration of labor: whether it is the reduction of the fluid content of the musculature of the uterus, the greater softening of the lower segment of the uterus, a lowering of the threshold of the consciousness of uterine contractions, thereby decreasing the conscious duration of labor, or the greater frequency of Braxton Hicks' contractions resulting in more dilatation of the cervix prior to the onset of labor, or

The method for determining pelvic depth, which is proposed herewith, should be accepted with precisely the same reservations and qualifications. That is, we consider it an accurate method which supplies valuable data. We are not proposing it as a substitute for clinical observation and judgment.

TECHNIQUE

Pelvic depth can be determined from the pelvicephalograms made for the purposes listed above, no special additional exposures being required. Three sites were used for the determinations, the forepelvis, the posterior-pelvis, and the pelvic canal, and

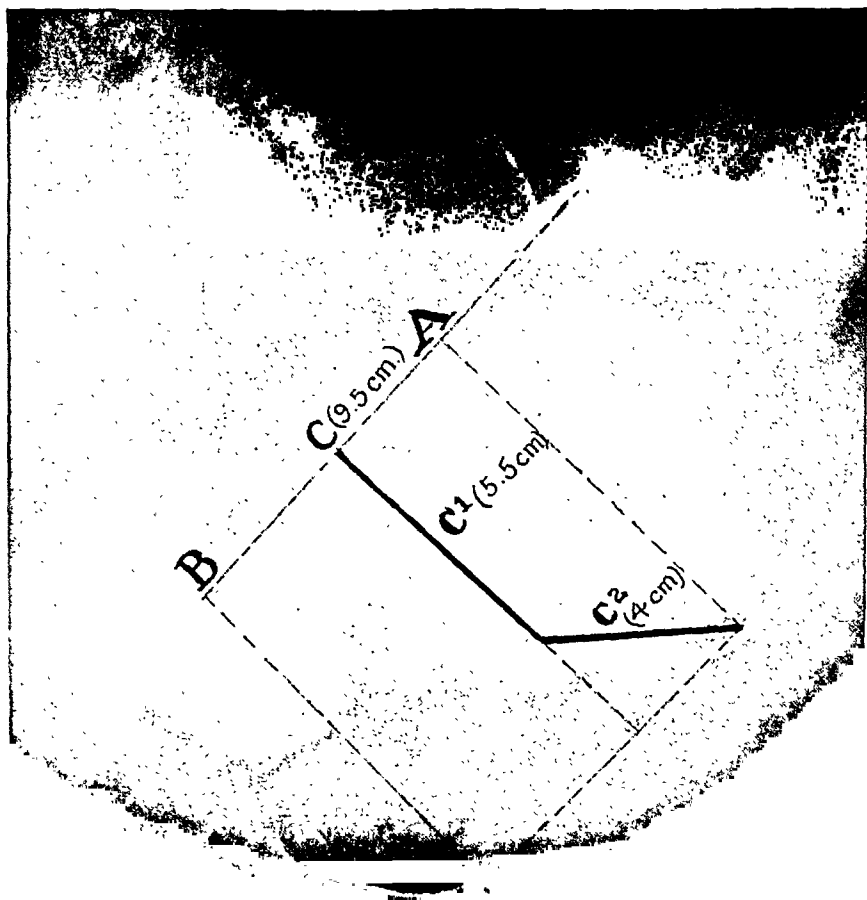


Fig. 1.—Pelvicephalogram of primipara with shallow pelvis. Note the shallowness of the pelvis (line C) and the difference in distance from the inlet to the spines (C_1) and from the spines to the outlet (C_2). The patient delivered a child weighing $7\frac{3}{4}$ pounds after a two-hour labor.

it was determined by comparative studies that measurements of the pelvic canal furnished the most accurate and valuable data. Whatever site is used, the measurements are made from the lateral film. The anterior film furnishes the correction factor; since all measurements on the lateral film are in the same plane, the same correction is necessary as is necessary in the estimation of the true conjugate.

1. When the forepelvis is used as the site of measurement, the pelvic depth is represented by a line perpendicular to the true conjugate and drawn from the upper margin of the symphysis pubis to the plane of the pelvic outlet (Figs. 1 and 2, line A). This measurement closely approximates the pubotuberous measurement, which can be determined manually and which usually represents the shortest vertical height of the pelvis. The clinical value of a knowledge of the depth of the forepelvis

AN ACCURATE ROENTGENOLOGIC METHOD FOR DETERMINING PELVIC DEPTH

RUPERT E. ARNELL, M.D., WILLIAM F. GUERRIERO, M.D.,
NEW ORLEANS, LA., AND JAMES B. IRWIN, M.D., SAN FRANCISCO, CALIF.
*(From the Departments of Obstetrics and Gynecology of the School of Medicine of
Louisiana State University and Charity Hospital of Louisiana, New Orleans)*

IT HAS long been recognized that the distance from the plane of the inlet to the plane of the ischial spines and the distance from the latter point to the plane of the outlet, reveal wide individual variations. For that reason the terms "shallow pelvis" and "deep pelvis" have acquired a definite clinical significance. For the same reason the accurate determination of the distance which the fetus must descend through the bony pelvis is a matter of considerable clinical importance not only in patients who require operative intervention but also in patients who deliver spontaneously.

It is curious that, notwithstanding the admitted importance of a knowledge of the depth of the true pelvis, no satisfactory precision method for determining it seems to have been suggested. Textbooks of obstetrics usually state that pelvic depth can be estimated from the impressions derived from vaginal examination, but this is in no sense a satisfactory method. Furthermore, such impressions are fundamentally erroneous because of the introduction of the personal equation, quite aside from the fact that such value as they possess is entirely dependent upon the clinical experience of the examiner.

So far as we have been able to determine, Schuman¹ has published the only method on record in the literature for obtaining the measurement of pelvic depth. By his method the perpendicular distance from the inferior surface of the ischial tuberosity to the superior border of the ramus of the pubis is determined by means of an ordinary pelvimeter. In his cases the average clinical measurement of the pelvic depth was 11.5 cm. and the average bony measurement, after due allowance for pubic and gluteal soft tissues, was 10.5 cm. Schuman emphasized the importance of this measurement and stated that increased pelvic depth was the most important characteristic of the male, funnel, or high assimilation pelvis.

The method for determining pelvic depth which we are describing in this communication was devised in the course of an investigation of the clinical value of the Ball technique of pelvicocephalography. Following preliminary studies,² we analyzed 503 selected cases³ studied by this method in regard to pelvic architecture, pelvimetry, fetometry and fetopelvic relations. Our conclusion was that when due regard was paid to clinical considerations and to those intangible factors which, even more than mechanical considerations, determine the course of labor, Ball pelvicocephalography is a very useful procedure, in that it warns the obstetrician, accurately in most instances, of possible mechanical risks and difficulties to be expected during labor and at delivery.

DATA IN 100 CASES

In 100 consecutive cases studied by the method described, the average pelvic depth was 11.97 cm., with 15 cm. and 8.2 cm. the upper and lower limits. The difference between the deepest and shallowest pelves, 6.8 cm., is surprisingly wide. The great majority of cases, 72, measured from 10.1 to 13.1 cm. The pelvic depth was between 8.1 and 9 cm. in 4 cases; between 9.1 and 10 cm. in 5; between 10.1 and 11 in 19; between 11.1 and 12 in 31; between 12.1 and 13 in 22; between 13.1 and 14 in 12; and between 14.1 and 15 cm. in 7 instances.

In addition to making information available as to total pelvic depth, the method we have proposed supplies data concerning the relationship of the ischial spines to the inlet and outlet of the pelvis. This relationship is subject to marked variations. In the 100 cases studied, the average distance of the spines from the pelvic inlet was 7.3 cm., and the average distance from the spines to the pelvic outlet was 4.67 cm. Greater variations occurred in the relationship of the spines to the inlet than to the outlet.

This relationship is important because the station (degree of descent) of the presenting part is determined from these land marks. Generalizations as to station are not satisfactory, because individual variations make it necessary to individualize in each case the degree of descent of the presenting part. If the ischial spines are a relatively short distance from the inlet, for instance, as when C_1 is less than usual (Fig. 1), the presenting part may not actually be engaged when it reaches the level of the spines. On the other hand, when C_1 is greater than usual (Fig. 2) and the ischial spines are relatively far from the inlet, the presenting part, when it reaches this plane, would be deep in the pelvis and well engaged.

The accuracy of the method has been checked on cadaveric material, and the errors revealed have been consistently less than ± 0.15 cm. We are presently engaged in correlating the type of labor and delivery with the factor of pelvic depth in the 100 cases studied and shall report these data elsewhere.

SUMMARY AND CONCLUSIONS

1. An accurate determination of pelvic depth is a valuable adjunct to pelvic measurements as they are now taken. Data concerning the relationship of the ischial spines to the planes of the inlet and outlet of the pelvis are also of value.

2. A precision method of securing these data is afforded by the use of Ball pelvicocephalograms. The method of securing the measurements is described.

3. The average depth of the pelvic canal in 100 consecutive cases was 11.97 cm. The variation was considerable, the shallowest and deepest pelves being, respectively, 8.2 cm. and 15 cm. in depth.

4. In the same 100 cases the average distance from the pelvic inlet to the ischial spines was 7.3 cm., and from the ischial spines to the outlet 4.67 cm. Considerable variations occur in the distance from the inlet to the spines, but the variations in the distance from the spines to the outlet are less marked.

REFERENCES

- (1) Schuman, W.: AM. J. OBST. & GYN. 28: 497, 1934. (2) Guerriero, W. F., and Smith, W. L.: New Orleans M. & S. J. 91: 299, 1938. (3) Guerriero, W. F., Arnell, Rupert E., and Irwin, J. B.: South. M. J. (In press.)

is lessened by the fact that the fetal head does not descend in this far anterior location. The measurement also does not make any correction for the changes in depth which usually occur in the posterior aspects of the pelvis and which occur more commonly in the male type of pelvis.

2. When the posterior pelvis is used as the site of measurement, the pelvic depth is represented by a line drawn from the sacral promontory to the sacrococcygeal articulation (Figs. 1 and 2, line *B*). This measurement is dependent upon the length and curvature of the sacrum, and therefore is the chord of the arc described by the sacrum rather than the true pelvic depth. The measurement is of even less value, furthermore, because the inclination of the sacrum is of more importance than its height. Two pelves, for example, may have sacra of equal length and curvature. In one the sacrum is directed backward and the pelvis is therefore adequate. In the other, the sacrum points sharply forward, encroaching on the outlet and thus producing an inadequate pelvis.



Fig. 2.—Roentgenogram of the pelvis of a primipara. Note that the pelvic depth (line *C*) is considerably greater than the pelvic depth in Fig. 1. Note also the increased depth from the forepelvis to the posterior pelvis. Fourteen months before this study was made the patient delivered a child weighing seven pounds after a sixteen-hour labor.

3. When the pelvic canal is used as the site of measurement, two determinations must be made. A perpendicular line is drawn from the true conjugate to the midpoint of the diameter between the ischial spines (Figs. 1 and 2, line *C*¹). A second line is drawn from the midpoint of the biischial spinous diameter to the midpoint of the transverse diameter of the outlet (Figs. 1 and 2, line *C*²). The total depth of the pelvic canal (*C*) is the sum of line *C*¹, which is the distance from the inlet to the midplane of the pelvis, and line *C*², which is the distance from the midplane to the pelvic outlet.

The third of these measurements, in our opinion, is a more accurate index of pelvic depth than either of the first two because it represents the approximate distance the fetal head must descend through the true pelvis. This measurement also furnishes useful information concerning the relationship of the midplane (spines) to the inlet and outlet of the pelvis.

Examination of the eyes revealed a widening of the palpebral fissures with a marked degree of exophthalmos. There was lagging of downward movement of the upper lids with downward gaze. The power of convergence was poor. Both pupils were dilated, reacted well to light, but sluggishly to accommodation. Both discs were edematous, two diopters elevation in the right and four in the left. The retinal veins were dilated and small hemorrhages were noted around both optic discs. The conclusion was that the patient was suffering from increased intracranial pressure plus definite evidence of an exophthalmic goiter.

Examination of the neck showed the presence of a uniformly enlarged thyroid gland and measurement over the gland was 12 inches (30 cm.). Examination of the chest showed the lungs to be entirely negative to auscultation and percussion. We may add, at this point, that at no time during this illness were there symptoms referable to the respiratory system. The heart was negative except for a persistent tachycardia.

Examination of the abdomen was negative except for the presence of a nontender, movable mass situated in the right lower quadrant immediately above the inguinal ligament.

Pelvic examination revealed a moderately relaxed perineum. The cervix was somewhat hypertrophied, softer than normal and the external os was irregular in outline and freely movable. The uterus was anterior, softer than normal, about the size of a two-month pregnancy and freely movable. To the left of the uterus was readily palpated a nontender, movable mass about the size of a plum. To the right was felt a larger mass which corresponded to the mass felt on abdominal examination and seemed to be about the size of an orange. Neurologic examination revealed a bilateral optic neuritis, right hemiplegia, diffuse, lower, motor neuron involvement as disclosed by the presence of atrophy, loss of the deep reflexes, and a bilateral Babinski. The conclusion reached by the examining neurologist was that we were dealing with a widely diffused, metastatic condition involving the brain and cord and that there was present both upper and lower neuron involvement, one lesion being located in the left motor area and another in the left parietal region.

Laboratory Findings.—Urine, repeatedly negative. Blood: On admission, hemoglobin 73 per cent (Sahli), red blood count, 3,300,000; white blood count, 6,300, of which 76 per cent were segmented neutrophils. Subsequent examinations showed a steady drop in the red blood cell picture, the hemoglobin falling to 35 per cent on November 6. The red cells showed marked anisocytosis, central achromia, and polychromatophilia. Wassermann and Kahn reactions were negative; blood chemistry showed normal values. Basal metabolism, plus 28 on Oct. 20, 1934, and plus 17 on Oct. 31, 1934.

The electrocardiogram showed the presence of sinus tachycardia with slurring of the QRS complex in all leads and a tendency to right ventricular preponderance. The conclusion was that the patient showed definite evidence of myocardial disease.

X-ray Examination.—In view of the possibility in the differential diagnosis that we were dealing with a case of chorionepithelioma with metastases, an x-ray of the chest revealed, through the lungs, numerous round metastatic nodules of varying sizes, suggestive of chorionepithelioma.

Hormone Findings.—The presence and amount of anterior pituitary-like substance in the urine were determined by the use of a modification of the Aschheim-Zondek test. The titer of the hormone present was estimated quantitatively, and the results obtained may be summarized as shown in Table I.

Friedman tests were carried out on 10 rabbits. Amounts corresponding to 0.01 c.c. of whole urine gave positive reactions in rabbits as compared with 10 to 12 c.c. used in the routine diagnosis of pregnancy. The reaction was much more pronounced than usually seen in normal pregnancies: The ovary resembling a cluster of bright-red cherries. The "blutpunkt" remained conspicuous for more than six weeks following injection. One of the rabbits was laparotomized ten weeks following injection, and it was seen that both ovaries were the seat of

CHORIONEPITHELIOMA OF THE UTERUS

WITH THYROTOXICOSIS, PRONOUNCED HORMONE TITER, AND DEATH FROM
INTRA-ABDOMINAL HEMORRHAGE

IRVING SMILEY, M.D., AND ALFRED B. CLEMENTS, M.D.,
NEW YORK, N. Y.

(From the Department of Gynecology and Pathology of The Bronx Hospital)

MRS. F. K., aged 27 years, was admitted to the Bronx Hospital on the service of Dr. Smiley with the following history: She had been married 7 years, and had had a spontaneous delivery of a living child five years ago. In August, 1933, she complained of vaginal bleeding, of about two weeks' duration, after having skipped one period, and, on the thirtieth of that month, she aborted. (It was only after she had been in the hospital ten days during her present illness that we were able to ascertain the fact that the material expelled at that time had resembled a cluster of grapes, and that the ambulance surgeon who was called to transfer her to the hospital had called it a mole.) She was removed to one of the neighboring hospitals where she remained for a period of ten days. Because of the continuous bleeding, she was curetted. The curettings consisted of practically normal endometrium. The bleeding stopped, and she was discharged several days later apparently cured, although somewhat pale and underweight.

Her general condition gradually improved, and her menstrual periods returned to a normal condition by October, 1933. She gained weight and considered herself perfectly normal in all respects.

Present Illness.—Her last menstrual period was June 29, 1934. She had complained of frequent attacks of headaches, nausea, and vomiting in the early part of August, 1934. In the latter part of that month there was slight staining which lasted for about two days. Becoming quite apprehensive about the possibility of another abortion, she sought medical advice and was assured that she was pregnant and that, with rest in bed, the pregnancy would continue. The slight bleeding did stop and she felt well until the morning of Sept. 6, 1934, or about nine weeks after the cessation of her last period, when she was awakened by a severe attack of vomiting. Within a short time she lost the power of speech, followed soon after by complete loss of motion of both right extremities. She became semicomatose, in which condition she was removed to the same hospital where she had been curetted. She improved somewhat under general care, regaining some power of motion in the hand and foot and was able to understand what was said to her, though still unable to speak.

She left the hospital on Oct. 6, 1934, of her own volition. The hospital diagnosis (communication) at the time of her discharge was "cerebral hemorrhage of a nontraumatic origin and pregnancy of two months' duration." The following positive findings were reported: (1) Positive Aschheim-Zondek test. (2) Spinal fluid examination showed the presence of xanthochromatism with increased spinal pressure. (3) Ophthalmic examination revealed the presence of a slight papilledema of the left eye (2 diopters). X-ray examination of the chest was negative. She remained at home until Oct. 17, 1934, where she was seen by one of us (I. S.) and immediately transferred to the Bronx Hospital.

Physical examination at this time revealed a young, white female, acutely ill, very anemic and showing evidence of loss of weight. The temperature was 100° F., pulse about 140, and respirations 24. There was present a very anxious expression, an inability to talk, and a flaccid paralysis of both right extremities. A marked tremor of the left hand was very prominent.

what laterally, the uterine musculature gradually widening as it approached the cervical canal. A smaller secondary mass, measuring 5 mm., was noted on the anterior uterine wall. The larger uterine tumor lacked the red, infarct-like appearance of the metastatic tumors in the other organs. The small remaining portion of the uterine canal exhibited an edematous, necrotic endometrium.

Both kidneys were the seat of numerous small and large oval encapsulated masses, the largest measuring 1.5 cm. These were dark and hemorrhagic and had the general appearance of fresh infarcts. Branches of the renal vessels reaching these areas appeared to be blocked with tissue resembling the secondary tumors. The central portions of some of these infarcted areas were distinctly necrotic.

The spleen measured 18 by 18 cm. in size and was markedly congested. There were numerous subcapsular, reddish brown, circumscribed areas, measuring 2 to 3 cm. Near one pole there was seen a large hemorrhagic infarct occupying almost one-third of the organ into which could be traced one of the main branches of the splenic vein. This was thrombosed with tumor material which extended into its finest ramifications. In the center of the intact portion of the spleen, there was seen a mass measuring 3 cm. and numerous smaller, irregular areas of hemorrhage. The central zone of each metastatic tumor was necrotic.

The liver was 26 by 17 cm. in size and the seat of several reddish nodules situated chiefly under the capsule and projecting above its surface. These masses varied in size from 2 to 3 cm., were friable and hemorrhagic and the vessels leading to them were occluded by tumor thrombi.

The serosal aspect of the mid-ileum was the seat of 3 firm, hemorrhagic, oval tumor masses, each having depressed centers corresponding to areas of necrosis. Each mass measured approximately 2.5 cm. in its largest diameter and extended through the wall of the bowel. The main branches of the superior mesenteric vessels appeared to be free of thrombi. Six similar, but smaller and more superficial, nodules were scattered on the serosal aspect of other portions of the ileum.

The anterior portions of the bodies of the third and fourth lumbar vertebrae appeared to be softened and hemorrhagic.

The lungs were studded with innumerable small and large dark red nodules, varying in size from a few millimeters to 6 cm., the larger ones being situated near the bases. The masses projected prominently above the surface of the lung. Both lower lobes were so extensively involved that hardly any intact pulmonary tissue remained. Upon section, the nodules were dark red, hemorrhagic, and well demarcated while the intervening, uninvolved tissue appeared quite normal.

The brain exhibited two major areas of hemorrhagic infarction with thrombosis of the lenticulo-striate and lenticulo-optic branches of the middle cerebral artery. The larger area measured 5 by 2.5 cm. and occupied the greater portion of the anterior half of the left cerebral hemisphere. The smaller measured 1.5 by 1.5 cm. and was situated in the left parietal lobe, 2.5 cm. distant from the longitudinal sulcus; Broca's and Wernicke's areas were within the thrombosed sites. The pituitary gland was yellowish in color and measured 1.5 by 0.8 cm.

Microscopic Pathology.—The histopathology was essentially that of a rapidly growing tumor, relatively small at the point of inception in the uterus but infiltrating vascular channels and producing extensive local and metastatic thrombotic and hemorrhagic areas. The uterine tumor exhibited narrow and broad irregular anastomosing strands of acidophile syncytial cells, some multinucleated, and islands of smaller, paler-staining Langhans cells with more definite cell outline. The stroma was sparse and irregularly distributed and deposits of fibrin were interspersed between the masses of actively growing neoplastic tissue. There appeared to be a definite zone of productive inflammation in and about the strands of invasive tissue. The tendency to vascular infiltration was not marked in the uterine tumor, so that thrombosis and hemorrhagic infarction were much less prominent than in any of the secondary tumors. However, occasional small scattered areas of necrotic tissue might be seen. The musculature was broken up by advancing tumor cells but complete penetration had not as yet occurred. Sections taken from the small

TABLE I. PROLAN DETERMINATIONS

DATE	PATH. NO.	MOUSE UNITS/LITER OF URINE	RESULTS
10/26/34	6482	2,000	Reaction 2 and 3
		3,000	Reaction 2 and 3
		4,000	Reaction 2 and 3
10/31/34	6504	6,000	Reaction 3
		8,000	Reaction 3
		10,000	Reaction 2 and 3
11/ 5/34	6549	1,000,000	Reaction 3
		1,500,000	Reaction 3
		2,000,000	Reaction 3

extensive corpora lutea formation. Such prolonged ovarian effect has, to our knowledge, never been reported previously.

Progress.—Her pulse rate was inconstant, ranging between 120 and 160 per minute, usually remaining about 140. The highest elevation of temperature reached was 101.5° F. and the respirations remained constant, about 24 to 26. She was fairly comfortable until several days before she died, when there were intermittent attacks of nausea and vomiting. There was marked improvement in her ability to use her arm and leg and she made many attempts to speak, succeeding finally in uttering a few words quite clearly. She appeared brighter, more cheerful and there was considerably less vomiting. The measurement of her neck showed a decrease of one-half inch in circumference.

In view of the patient's poor physical state, the involvement of her myocardium as evidenced by the electrocardiogram, the presence of marked hyperthyroidism and constant tachycardia, and the widespread dissemination of the tumor, it was felt that surgical treatment should be deferred. She was therefore transfused and given deep x-ray therapy.

Repeated vaginal examinations disclosed no change in the size of the uterus, total absence of any bleeding, but definite increase in the size of the masses palpated in both fornices. These tumors became irregular in outline, the one on the right reaching almost halfway to the umbilicus.

On November 3, the patient complained of pain radiating from the left shoulder to the elbow associated with abdominal cramps. This improved within twenty-four hours, but returned on November 6, when she became restless and gave the appearance of intra-abdominal bleeding, respirations became labored, and heart-beat very rapid and weak. Within an hour her skin was cold and clammy. The patient became pulseless and died in spite of stimulation. Permission for a post-mortem examination was obtained and a complete autopsy performed within two hours after death (by A. B. C.).

Autopsy Findings.—The relevant necropsy findings were as follows: Upon opening the peritoneal cavity, there was seen approximately 1,500 c.c. of bloody fluid with several large clots in the lateral gutters and behind the liver. The uterus appeared to be enlarged, measuring 9 by 7 cm. in its largest diameters. No tumor or other abnormality was noted on its outer surface. The peritoneal reflection showed no gross pathology. The appearance of the ovaries, however, was very striking. Both were greatly enlarged, nodular, and cystic, the right being greater in its largest diameters than the uterus, measuring 10.5 by 7 cm. The left ovary measured 8 by 6 cm. Both ovaries were very similar in appearance, being the seat of many small and large lutein and hemorrhagic cysts. One of the latter, in the right ovary, measuring 1.5 cm. in its longest diameter, had recently ruptured and was filled with blood clot. This was evidently the source of the blood found free in the peritoneal cavity. Upon opening the uterus, there was found a large, reddish brown, friable mass measuring 5 by 4 cm. which occupied almost the entire body of the uterus but was situated toward its upper and posterior portions. The demarcation of the tumor mass from the uterine wall could be discerned quite clearly. The latter was compressed to a very thin layer, particularly near the upper pole and some-

The kidney sections exhibited, perhaps, next to the lungs, the most extensive thrombotic areas. One could often discern the hemorrhagic area clearly encompassed by venous wall and not infrequently intramural nests of tumor cells which, in places, had reached the adventitia. Here and there one might note small sheets of syncytium and Langhans cells which appeared to be actively growing through the hemorrhagic mass rather than having been merely caught in its meshes. The apparent absence of any definite stroma suggested its local source of nutrition. The renal parenchyma adjacent to this area was compressed, atrophic, and infiltrated with nonneoplastic wandering cells. Many of the glomerular tufts were completely thrombosed by small emboli of tumor cells so that all one saw was a round or oval area of clear serous material capped at one end by a tiny nidus of tumor tissue. The whole was shrunken away from the parietal layer of the capsule. The affected glomerular beds were several times the size of adjacent normal ones. The interstitial tissue was infiltrated by wandering macrophages (Fig. 2). Invasion of the larger renal vessels by neoplastic cells was also seen, the vessel itself being thrombosed, tumor tissue having apparently penetrated and destroyed the intima. The invading sheet of Langhans and syncytial cells appeared to have been obstructed, temporarily at least, by the media against which it was flattened. The advancing growth then spread in a circumferential fashion, the contiguous muscularis having been thinned out. Infarctions produced as a result of this process were numerous and varied in size from a few millimeters to several centimeters.

The cells of the adrenal cortex were hypertrophic and granular and the nuclei were pyknotic and prominent. The stroma was sparse and, in places, definitely separated by clear spaces from the cell cords. The thyroid presented a rather unusual appearance of large acini distended with colloid with low cuboidal to flattened epithelium alternating with smaller, more cellular, areas practically devoid of colloid. No acinar spurring was noted, and there was a distinct diffusely lymphoid stroma. No necrosis, hemorrhage, or calcific deposits were noted.

The pituitary exhibited numerous large chromophobe cells regarded by Novak and others as characteristic of gestation. In the sections examined, these cells did not appear to outnumber the basophiles which Stockl regards as associated with an increased secretion of the gonadotropic hormone and secondary to the chorion-epithelioma. Nor did the chromophobes appear to be greatly in excess over the eosinophiles which are regarded by Philipp as associated with hypersecretion of the pituitary. From a careful examination of many sections, it might be said that the chromophobe cells stand out very prominently by reason of their hypertrophy rather than because of an actual marked increase in their number.

SUMMARY

The above case was one of chorionepithelioma of the uterus with extensive metastatic spread. The thyrotoxic symptoms, the lutein cysts of the ovary, the tremendous hormone titer, and the mode of death by intra-abdominal hemorrhage were but a few of the outstanding features present.

We are indebted to Dr. Joseph Felsen for the pathologic studies and the photomicrographs.

remaining area of what appeared to be intact endometrium adjacent to the tumor mass revealed extensive necrosis with evidence of local extension of the neoplastic process. No normal endometrium could be seen nor definitely identified.

Sections from the lung exhibited extensive foci of thrombosis, necrosis, and hemorrhage with contiguous areas of exudative, reactive inflammation. The typical picture was a central core of thrombosed, necrotic tissue consisting chiefly of cellular detritus, fibrin, and red cells, outside of which was a sinuous border made up of macrophages capped by a broader, irregular zone of intact neoplastic tissue. The stroma was extremely scant and the adjacent normal pulmonary tissue was atelectatic. Some alveoli were filled with inflammatory exudate. The individual tumor masses were so numerous that comparatively little pulmonary tissue remained intact. In some places one might discern actual invasion of and spread through the alveolar wall with almost complete filling of the air vesicle by tumor cells. More or less hemorrhage accompanied the process in each case (Fig. 1).



Fig. 1.

Fig. 1.—Invasion of wall of pulmonary alveolus by tumor tissue.



Fig. 2.

Fig. 2.—Tumor emboli in kidney.

The liver was the seat of extensive focal and coalescent thrombotic areas with apparently viable tumor tissue, however, always visible at the periphery. In some sections invasion was definitely limited to the portal canal, but this appeared to be merely an early stage of the same process, giving rise to larger areas of coalescent tumor tissue seen elsewhere. Invasion of the vascular channels was very pronounced and, as adjacent lobules were invaded by neighboring tumor masses, the intervening hepatic parenchyma was compressed and atrophic. The sinusoids appeared to be wider than normal and the reticulum more prominent, but this might be more apparent than real by reason of the narrowing of the liver cords. In many places the cells of Kupffer stood out prominently.

and atypical mitotic figures. The nuclei were hyperchromatic and contained large nucleoli in every field. One such region is shown in Fig. 3 in which the lesion has reached the stage of epithelioma in situ (Broders). Finally, several

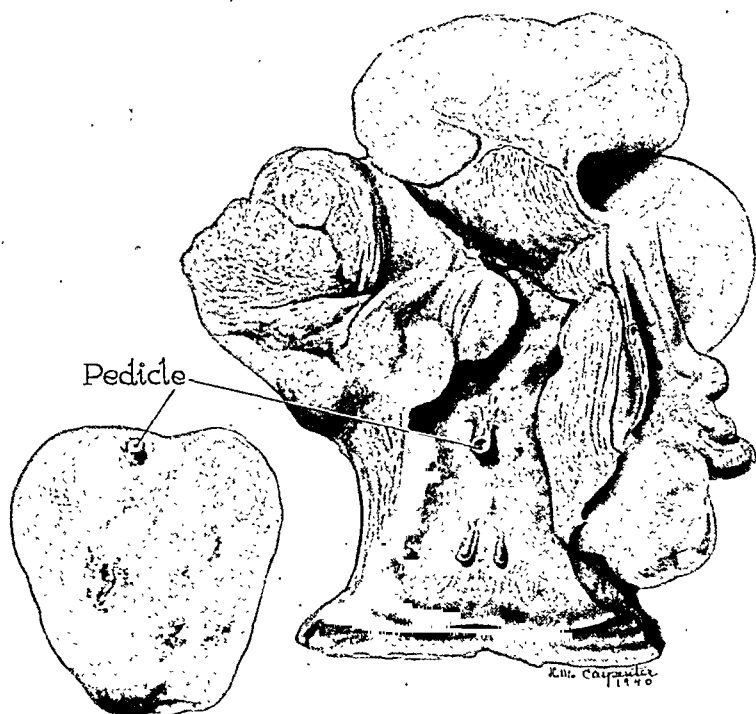


Fig. 1.—Gross specimen showing pedicle of fibromyoma around which the epithelioma was localized.



Fig. 2.—Hyperplasia of squamous epithelium covering fibromyoma in vicinity of pedicle ($\times 52$).

UNUSUAL COEXISTENCE OF SQUAMOUS CELL CARCINOMA AND CERVICAL FIBROMYOMA*

MALCOLM B. DOCKERTY, M.D., AND JAMES C. MASSON, M.D.,
ROCHESTER, MINN.

(From the Mayo Clinic)

UTERINE fibromyoma and uterine carcinoma both constitute a fair proportion of gynecologic lesions, and it is not surprising that these two conditions are encountered occasionally in combination. According to Martzloff⁷ in a study of more than 16,000 cases of uterine fibromyoma, carcinoma of the corpus uteri was present in 2.23 per cent and of the cervix, in 1.5 per cent. However, since cervical fibromyomas constitute but 5 per cent of the entire group and since pedunculation is the exception rather than the rule, the coexistence of squamous cell carcinoma in such a case becomes a matter of extreme rarity. When the malignant process is confined to the stalk of the fibromyoma, we have a combination of circumstances bordering on the unique. In the literature, however, we encountered articles by Bishop,¹ Chisholm,⁴ Geller,⁵ Princeteau⁸ and Stein,⁹ describing cases comparable in many respects to the one we wish to report.

REPORT OF CASE

A single white woman, aged 56 years, came to the Mayo Clinic on Feb. 13, 1940; she complained of daily, vaginal, postmenopausal spotting of ten years' duration. For nine years she had followed the counsel of a "friend" who had advised against medical consultation but finally the patient compromised by consulting an osteopath who made a diagnosis of "fibroids" and advised operation.

Examination disclosed an enlarged, somewhat tender uterus which was apparently the seat of multiple fibromyomas. The largest of these appeared to be pedunculated, of cervical origin and somewhat infected. Results of examination otherwise were essentially negative.

At operation on Feb. 17, 1940, a pedunculated fibromyoma that measured 7 cm. in diameter was removed vaginally by one of us (Masson). The unusual condition to be described herein was found on routine fresh frozen sections stained with polychrome methylene blue. Under ordinary conditions, we do not like to open the abdomen for at least a couple of weeks after removing an infected fibroid through the vagina, but on account of the diagnosis of malignancy we felt that we should not wait that long in this case, and three days following the first operation, after thorough sterilization of the vagina, cervix, and raw surface from which the fibroid had been removed, we did a total abdominal hysterectomy. After a convalescence complicated by a mild infection of the upper portion of the respiratory tract, the patient was given a course of roentgen therapy over the pelvis and was dismissed on the thirtieth postoperative day.

Gross features of interest are shown in Fig. 1. Microscopic sections taken through the convexity of the pedunculated growth revealed the usual picture of a hyalinizing fibromyoma with a subacute inflammatory reaction in the superficial layers. Study of a region in the vicinity of the stalk, however, demonstrated a mantling of stratified squamous epithelial cells, somewhat hyperplastic in appearance (Fig. 2). Toward the attachment of the pedicle, the epithelial cells became more irregular in size and shape, giant cell forms were frequently encountered and pronounced cellular activity was evidenced by numerous typical

*Submitted for publication, May 8, 1940.

being peculiarly confined to the stalk of the pedunculated fibromyoma, as already described. The tubes and ovaries were atrophic.

COMMENT

Considerable literature has accumulated on the subject of cellular metaplasia since Küstner,⁶ in 1884, called attention to the squamatization occasionally observed in connection with cervical polyps. The roles of long-continued irritation and infection have been repeatedly stressed as etiologic factors in the production of this metaplasia which has long been considered in the light of a definitely precancerous condition. Thus, it is pointed out, arise squamous cell carcinomas of the gall bladder and bronchial mucosa, situations in which squamous epithelium is not normally found. It is not surprising, therefore, that metaplasia is en-



Fig. 5.—Columnar epithelium lining the cervical canal ($\times 32$).

countered frequently in the uterine cervix. Here, trauma, infection, and, frequently, ulceration occur in combination in a region in which squamous cells and glandular epithelium are normally in intimate approximation. It is thus that we attempt to explain in our case the progression through prolonged ulceration, repeated repair and metaplasia to the final stage of malignant neoplasia. The localization of the latter serves merely to emphasize the importance of the etiologic factors and points to the necessity for early treatment of certain benign lesions of the uterine cervix.

SUMMARY

An unusual case of coexistent polypoid cervical fibromyoma and early squamous cell carcinoma is reported. Evidence is adduced that trauma and prolonged chronic irritation led to atypical repair, metaplasia, and eventually to malignant neoplasia.

REFERENCES

- (1) *Bishop, Elliott*: AM. J. OBST. & GYNEC. 12: 284, 1926. (2) *Broders, A. C.*: J. A. M. A. 99: 1670, 1932. (3) *Idem*: Personal communication to the authors. (4) *Chisholm, A. E.*: Practitioner 110: 320, 1923. (5) *Geller, F. C.*: Zentralbl. f.

regions were seen in which the basement membrane was broken and migration superadded to fulfill the most exacting criterion of undoubted malignancy, an invading squamous cell carcinoma, Graded 3 (Fig. 4). Careful examination of the

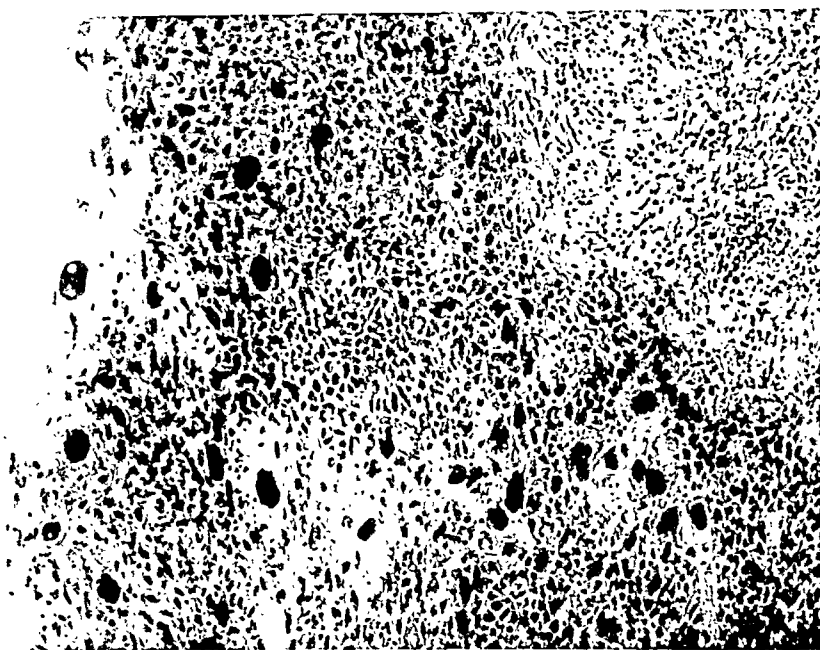


Fig. 3.—Squamous cell carcinoma, Grade 3, in situ. Note hyperchromatic cells with giant nuclei ($\times 95$).



Fig. 4.—Infiltrating squamous cell carcinoma, Grade 3 ($\times 95$).

tissue removed at the second operation revealed multiple uterine fibromyomas, cystic endometrium and several small adenomatous cervical polyps. The epithelial lining of the cervix was columnar as far down as the external os (Fig. 5). No trace of carcinoma could be found anywhere in the uterus, the malignant lesion

unusual experience of having encountered 4 cases of mechanical intestinal obstruction, 3 ante partum and 1 post partum, seems to warrant this report.

CASE REPORTS

CASE 1.—S. S., 41 years of age, para ii, was admitted to the hospital on Sept. 1, 1938. Two spontaneous deliveries, one in 1923 and the other in 1926, and a laparotomy in 1931 for the removal of a left benign ovarian cyst are noted in her history. On admission she was about six weeks before term, and had had irregular labor pains for several hours. Rectal examination disclosed a high breech presentation impressible into the pelvis, and a cervix two fingers dilated and uneffaced. The fetal heart sounds were normal and occasional uterine contractions palpable.

Irregular pains continued until the following morning when, after a few hours of nausea, belching, and retching, there followed an attack of vomiting, and colicky pains in the epigastrium. There was no evidence to indicate a toxemia of pregnancy. By afternoon of the same day all symptoms had spontaneously subsided.

The next day (September 3) marked an episode of recurring epigastric colic, much distention, tenseness, and pain over the epigastrium. The temperature was 102° F. By gastric lavage 1,000 c.c. of dark brown, foul-smelling fluid was recovered. An enema gave a poor result though the patient had had no bowel movement since admission.

Twenty-four hours later (September 4) all symptoms subsided and the abdomen was soft and flat. The rectal temperature was 100° F. Occasional uterine contractions occurred, but the cervix was still two fingers dilated. The impression was constriction by post-operative adhesions of an incomplete type with spontaneous recession.

Since the patient was obviously not in labor, she was transferred on September 5 to the medical service. For the next three days her symptoms remained quiescent and her temperature 99° to 100° F. She was passing some gas and small quantities of feces. On September 8 her temperature rose to 102° F., fecal vomiting suddenly occurred, and the abdomen became moderately distended.

A diagnosis of mechanical intestinal obstruction due to postoperative adhesions was made and operation advised. The family refused consent until the following day. The delay proved unfortunate, for during the subsequent twenty-four hours the patient lapsed into a condition of vasomotor collapse. Transfusions, intravenous glucose, gastric lavage, and other stimulating measures were employed, but she failed to rally sufficiently to attempt surgical intervention.

On the same day after several hours of pains, a male still-born infant was delivered spontaneously by the breech. The following day (September 11) she became comatose, temperature rose to 105° F., and at 11:25 A.M. she died.

Autopsy by Dr. Ravid disclosed partial intestinal obstruction with firm adhesions of the sigmoid to the left uterine cornu. It should be mentioned that after delivery there occurred naturally profound intra-abdominal changes and rearrangement of the intestinal loops and uterus. Hence, the pathologist's report of partial obstruction is at variance with conditions that existed ante partum. The mechanical effects on the intestine resulting from delivery will be more specifically discussed in connection with the second case.

Comment.—This case too well exemplifies the diagnostic pitfalls characterizing acute intestinal obstruction, particularly of the partial type, during late pregnancy. The difficulty was further accentuated by periods of recession of clinical symptoms. The improvement, objective and subjective, following lavage, enemas, and sedatives, is fraught with great danger as it induces a sense of false optimism. To wait for fecal vomiting before venturing a diagnosis is always injudicious and frequently belated. The lower the site of obstruction, the longer will be the interval before such vomiting appears.

Gynäk. 47: 406, 1923. (6) *Küstner, Otto*: Centralbl. f. Gynäk. 8: 321, 1884. (7) *Martzloff, K. H.*: In *Curtis' Obstetrics and Gynecology*, Philadelphia, 1933, W. B. Saunders Company, Vol. 2, p. 838. (8) *Princeteau, René*: Paris méd. 55: 555, 1925. (9) *Stein, Aritur*: Am. J. Surg. 10: 136, 1930.

RELEVANT ARTICLES NOT REFERRED TO IN TEXT

(1) *Barthélemy, M.*: Bull. Soc. d'obst. et de gynéc. 25: 164, 1936. (2) *Counseller, V. S., Cox, F. W., Church, G. T., and Paterson, Susanne J.*: S. Clin. North America 13: 959, 1933. (3) *Fruhmann, C. F.*: Northwest Med. 26: 244, 1927. (4) *Findley, Palmer*: AM. J. OBST. & GYNEC. 11: 450 and 519, 1926. (5) *Stone, W. S.*: Surg. Gynec. Obst. 23: 248, 1916.

ACUTE INTESTINAL OBSTRUCTION COMPLICATING PREGNANCY AND THE POST-PARTUM PERIOD

WITH A REPORT OF FOUR CASES

FREDERICK WEINTRAUB, M.D., AND BORIS JAFFE, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology and the Department of Surgery,
Israel Zion Hospital)

A REALIZATION of the possibility of acute intestinal obstruction occurring as a complication of the pregnant or parturient woman is an indispensable prerequisite to timely diagnosis and rational treatment. In early surgical intervention lies our main hope of effecting some reduction in the high mortality rate exacted by this rare and grave affection. Delay in diagnosis as well as indecision and perilous conservatism in management are all too frequently observable in case reports published both in this country and abroad. The first of the four cases, herein reported, which ended fatally, stimulated the present study and impressed us with the urgent need of readier recognition and more prompt treatment of this complication.

Three of the cases of acute intestinal obstruction during pregnancy occurred in a series of over 32,000 deliveries at the Israel Zion Hospital. The fourth case occurred post partum.

G. G. Bemis found this complication twice in 15,000 obstetric patients at the Woman's Hospital of New York. From 1900 to 1931 the American and British literature contains reports of only 13 cases. Kornfeld and Daichman in 1934 reported one case of volvulus in over 31,000 hospital deliveries and stated that a careful search of the literature failed to reveal any cases reported in this country up to that year. Casagrande in 1936 reported a case of full-term pregnancy complicated by acute intestinal obstruction and stated that two such cases of acute obstruction had occurred in 11,246 hospital cases. Stander in his 1936 revised edition of Williams' *Obstetrics* curtly disposes of intestinal obstruction as follows: "This rare complication of pregnancy should be treated upon general surgical principles." Similar cursory or no consideration is given to the subject in other standard American and British textbooks. In an excellently individualistic article on the "Surgical Complications of Pregnancy," Cosgrove mentions no case of acute intestinal obstruction in 25,000 obstetric patients on his service.

Most of the published reports on this subject are based on the individual author's observation of one, or occasionally two cases. The

CASE 3.—H. G., 28 years old, para 5, was admitted, when six months pregnant, on Oct. 21, 1939. Her chief complaint was the sudden onset of severe and generalized abdominal pains and frequent vomiting spells, no bowel movement, and no flatus during the preceding twenty-four hours. There was no toxemia. Physical examination revealed a left pararectal scar (ovarian cystectomy, 1937), generalized abdominal tenderness, and moderate distention. The impression was high intestinal obstruction. During the following forty-eight hours her symptoms became intensified.

A laparotomy under spinal anesthesia revealed an omental band wrapped around the lower part of the ileum, tightly constricting it. One foot of distended ileum was deeply cyanotic. Severance of the adhesions and hot applications restored the bowel color and lumen continuity. Uneventful convalescence and discharge from the hospital ten days after operation ensued.

Comment.—In this case, though there was evidence of a former abdominal operative scar, which should have served as a beacon, in the first place, and though there occurred a dramatic onset of all the cardinal symptoms of acute intestinal obstruction, viz., nausea, vomiting, abdominal pain, distention, and constipation, in the second, there followed nevertheless a delay of forty-eight hours before operation was performed.

CASE 4.—J. Y., 32 years old, para i, was admitted on Jan. 20, 1938, when seven months pregnant. In her history appears a record of a right salpingo-oophorectomy and appendectomy nine years previously, and of an umbilical herniorrhaphy four years previously. A normal delivery occurred eight years ago. Her chief complaint was vomiting of seven months' duration. In the first trimester of her pregnancy the vomiting had occurred only in the morning, but thereafter at any time of the day. There had been periods of comparative freedom from vomiting, lasting from a few days to several weeks.

For the entire week preceding hospital admission she had had no bowel movement. During the same week abdominal distress and distention had become marked and vomiting so frequent that it was impossible for her to retain any food. A diagnosis of intestinal obstruction was made. At operation adhesions involving the anterior abdominal wall, omentum, small intestine, and uterus were found. Many intestinal loops were adherent to one another, but the obstruction was caused by several bands constricting the small intestine. The bands were severed, the intestinal coils liberated, and part of the omentum removed. The postoperative course was uneventful and normal delivery at term ensued.

Comment.—The chief complaint in this case was chronic, intermittent vomiting of seven months' duration. Its occurrence in the forenoon, during the first trimester, was interpreted as the ordinary morning sickness of early pregnancy. Precisely when this type of vomiting ceased, and that caused by intestinal obstruction supervened cannot be stated. It may be assumed, however, that this occurred in the fourth month, for it is unusual for ordinary morning vomiting to become aggravated after this period in a patient not suffering from a toxemia. It was then that the vomiting in this case no longer remained limited to the morning but occurred at any period of the day. Furthermore, the abdominal scars and the history of two laparotomies should have directed attention to the possibility of an intestinal complication from adhesions. When one considers also that, during the fourth and fifth months, the uterus encroaches on the abdomen, the mode of production at this time of intestinal obstruction is understandable. During the first trimester, when the uterus is still within the pelvis, it is most rare for adhesions to give rise to serious symptoms. Beginning in the second trimester, the obstructive features persisted in this case until an acute culmination in the seventh month. The enlarging uterus, acting on old adhesions, supplied the mechanical basis for this development.

SUMMARY

1. Because of its rarity and the confusing influence exerted by co-existent pregnancy, acute intestinal obstruction complicating pregnancy is characterized by delay in diagnosis and belated surgical intervention.

CASE 2.—M. B., 35 years old, para ii, had a spontaneous delivery on the day of admission, Feb. 28, 1934. Her pregnancy had been normal. Two previous pregnancies and deliveries had also been normal. During the past ten years occasional episodes of constipation and right lower quadrant pain of varying severity, lasting several days at a time, appear in her anamnesis. A diagnosis of chronic appendicitis had been made.

Before she was removed from the delivery table, it was observed that her right upper and lower abdominal quadrants were considerably distended and tympanitic. This finding persisted through that day and the next; and, on the second day post partum, there occurred in addition to the tympanites, several vomiting spells and moderately severe pain in the right upper and lower quadrants. Her temperature rose to 102° F., pulse 110. On the third day post partum, her symptoms became aggravated. At no time since delivery had she passed any gas or feces.

On the fourth day post partum, fecal vomiting occurred. A diagnosis of obstruction in the transverse colon or its flexures was made. At operation, performed under spinal anesthesia the same day, the cecum, thinned-out and ballooned to the size and shape of a honeydew melon, thrust itself through the incision. The ascending colon was collapsed and surrounded by numerous adhesions in which a long, thin appendix was firmly imbedded. Near the center of the cecum a dark, hemorrhagic area, about one-half inch in diameter, was visible. As soon as the adhesions were liberated, the cecal distention diminished and passage of gas into the collapsed ascending colon occurred. A cecostomy was performed.

During the first five postoperative days, her course was stormy. Improvement was manifest by the tenth postoperative day when spontaneous defecation occurred though the colostomy was draining well. She was discharged twenty-one days after operation. Two months later the cecal fistula was closed surgically.

Comment.—This case demonstrates the possibility of acute mischief during the early post-partum period, arising from adhesions which remained relatively innocuous ante partum. The compression exerted by the enlarging uterus during the course of the pregnancy on the cecum and adherent ascending colon was a gradual process which did not disrupt entirely the patent relationship between these adjacent segments of bowel. It will be recalled that there is a normal tilt to the right and posteriorly of the pregnant uterus which produces increased pressure on the cecum and ascending colon. Immediately following parturition there occurred an extensive and widespread re-arrangement of the intestinal coils and a marked alteration in intra-abdominal and intra-intestinal pressure. As the cecum was suddenly decompressed by the abrupt emptying of the gravid uterus, it is conceivable that an inrush of gas would cause the cecum to distend and probably undergo a certain degree of torsion if there existed any obstruction at a higher level. Such obstruction could readily be brought about at this time by the rendering taut of the many adhesions previously mentioned which, by angulating and fixing the ascending colon with its short mesenteric attachment, would convert its previously patent lumen into an obstructive lesion. The greater the gaseous pressure within the cecum, the more tightly sealed would be the site of obstruction in the fixed ascending colon.

Bearing in mind the *modus operandi* of the obstruction, it will be understood why the patient's right upper and lower quadrants became markedly distended so soon after emptying of the uterus. In this case the diagnosis should have been made and operative treatment instituted earlier than the fourth day post partum, and before the onset of fecal vomiting since, unlike the previous case, the signs and symptoms were of a progressive nature, in the first place, and, in the second, the post-partum abdomen is more favorable for physical examination than the tense abdomen of late pregnancy or term. However, the opportunity for us to see the patient did not arise until the day of operation.

It is of interest to note that no previous operation had been performed upon this patient. The history of so-called chronic appendicitis or pelvic inflammation in suspected cases of acute intestinal obstruction in the post partum should be given due consideration.

BENIGN POSTIRRADIATION STRICTURE AND PRIMARY CARCINOMA OF THE COLON

JAMES N. STANTON, JR., M.D., AND HAROLD W. JACOX, M.D.,
PITTSBURGH, PA.

(From The Western Pennsylvania Hospital)

WITHIN the past six years attention has been called to the late occurrence of benign strictures of the sigmoid colon and the small intestine following radium and roentgen therapy for cancer of the cervix uteri.¹⁻³ The interval from irradiation to the appearance of symptoms varied from a few months to as long as eight years. The importance of differentiating between a recurrent malignant condition and a sequela of previous radiation therapy before giving further irradiation or before considering the condition hopeless due to recurrent or metastatic cancer was emphasized.³

The patient whose case we report presented such a problem about nine years after she received radiation therapy for a recurrent malignant lesion of the uterine cervix. However, not only a benign stricture of the upper sigmoid colon but also a second primary cancer of the bowel were discovered at laparotomy.

For the patient's past medical history we are indebted to Drs. Thomas S. Cullen and Curtis F. Burnam of Baltimore:

From Thomas Cullen's letter we have the following information: "On May 8, 1930, I saw Miss A. Z. S. of Pittsburgh. The patient was 43 years of age. She began to menstruate at 13 and was regular; flow was moderate, and she had had no pain until the year previous to her coming to see me. Her last period was two weeks ahead of time, and for a few weeks, on the least exertion, she would pass bright red blood from the vagina.

"During the World War she had amebic dysentery.

"On pelvic examination, a cauliflower growth, about 8 cm. in diameter, sprang from the cervix. It almost completely filled the vagina. Fortunately, it was confined to the cervix and was freely movable. The body of the uterus was relatively small. To the right of the uterus was a mass 7 or 8 cm. in diameter, freely movable, and possibly a cyst.

"On May 12, 1930, the patient was operated upon at the Johns Hopkins Hospital. A complete Wertheim operation was done. On the left side the ureter was rather difficult to get at, as there was a little inflammatory thickening in this area. The small ovarian cyst on the right side was removed before the hysterectomy was completed. The patient made a satisfactory recovery.

"The pathologic report was as follows:

"*Specimen.*—The uterus was normal in size and shape. The peritoneal surface was smooth. The cervix was attached, together with a cuff of vaginal mucosa. The latter was pale and smooth and measured about 1 cm. in width. The cervix was a cauliflower-like mass measuring 5.5 cm. in diameter. It was granular and very friable. The larger part of the growth was in the anterior lip, though the posterior lip was also involved. None of the growth seemed to have extended beyond the vaginal cuff.

"The cervix, uterus, left tube, and left ovary were not cut for section, but were saved as a whole for the museum, as a beautiful example of carcinoma of the cervix.

"The left tube and ovary were of about normal size and appearance, externally and on section.

"The right ovary was replaced by a cystic mass, 8 cm. in diameter. The peritoneal surface was pale and smooth. The tube was stretched across the surface of the cyst and was adherent to it. The cyst was unilocular and was filled with clear, straw-colored fluid. The wall measured about 2 to 4 mm. in thickness. The lining was pale and smooth.

"*Provisional Diagnosis.*—Epidermoid carcinoma cervix uteri. Unilocular, simple serous cystadenoma ovary, right. Normal tube bilateral. Normal ovary, left.

2. Three of the cases, herein reported, occurred during the antepartum period in a series of over 32,000 hospital obstetric admissions. The other occurred during the early post partum.

3. From a review of the 4 cases, one is impressed with the important fact that the single fatality of the group occurred in that patient who was not subjected to operation. In the other three cases the relative timeliness of operation was reflected in proportionately favorable results. It is obvious that *pregnancy predicates pernicious procrastination* in the management of this condition.

4. "Primary pregnancy ileus," as defined by previous writers, and its two types are mentioned. In contradistinction to "primary pregnancy ileus," we suggest the designation of "*secondary pregnancy ileus*" for those cases in which pre-existing bands or adhesions are primarily responsible for the obstruction, the mechanical effects of the enlarging uterus being the secondary factor in its production. All of our cases were of the secondary variety.

5. In a gravida who presents symptoms of acute intestinal obstruction, it is of paramount importance to look for the scar of a former laparotomy. In the absence of such scar, however, a history of abdominal or pelvic inflammation may be equally relevant. The commonest operative antecedents have proved to be appendectomy and pelvic operations.

6. Because one or several of the cardinal symptoms of acute intestinal obstruction are so commonly associated with normal pregnancy, they are generally regarded with a complacency that may prove dangerous or even disastrous in the presence of this complication. A discussion of these several symptoms with reference to differential diagnosis is given.

7. Improved maternal and fetal results can be achieved only by early operation. Only the minimal surgical procedure should be carried out that suffices for the relief of the obstruction. A meticulous technique whose objective is to avoid unnecessary disturbance of the pregnant uterus is indicated. Gratuitous surgery is contraindicated.

8. To delay operation during pregnancy in anticipation of spontaneous cure of acute obstruction is to court disaster. Until proved otherwise, each case is *prima facie* one of mechanical obstruction, or, as we term it, "*secondary pregnancy ileus*."

9. The exceptional instances in which preliminary cesarean section is indicated, are discussed.

We express our indebtedness to Drs. Leo S. Schwartz, Romeo Auerbach, and William L. Wolfson for permission to utilize the foregoing case records.

REFERENCES

- (1) Bemis, G. G.: AM. J. OBST. & GYNEC. 24: 436, 1932. (2) Casagrande, J.: Ibid. 32: 1058, 1936. (3) Kornfeld and Daichman: Ibid. 27: 768, 1934. (4) Stander, H. J.: Williams' Obstetrics, New York, 1936, D. Appleton-Century Co. (5) Slemons and Williams: West. J. Surg. 46: 84, 1938. (6) Cosgrove, S. A.: AM. J. OBST. & GYNEC. 34: 469, 1937.

Sigmoidoscopic examination was unsuccessful in reaching the lesion. Laparotomy was advised but the patient refused it. She left the hospital only to return within a month because of the recurrence of abdominal pain.

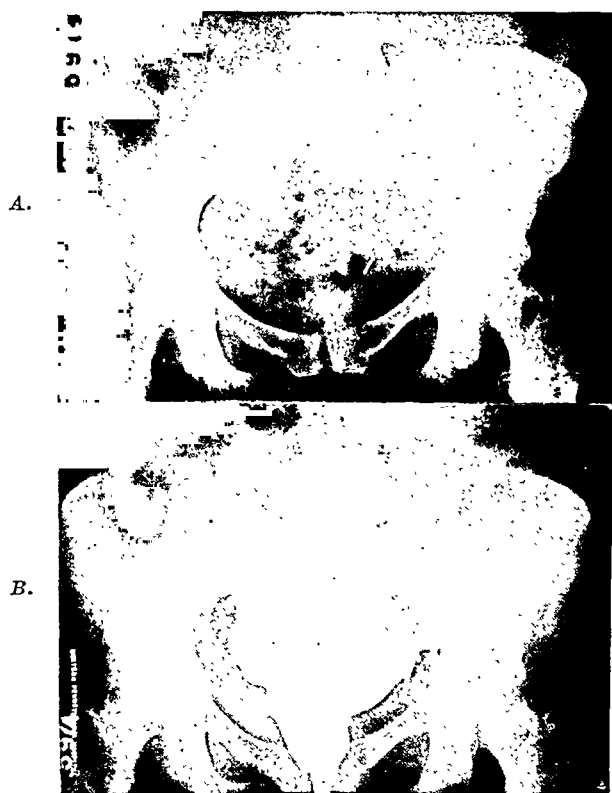


Fig. 1.—*A*, Roentgenogram of the pelvis with a metallic foreign body resembling a radon seed opposite the left ischial spine. *B*, Colon examination showing obstruction to the passage of barium at the junction of the descending and sigmoid areas.

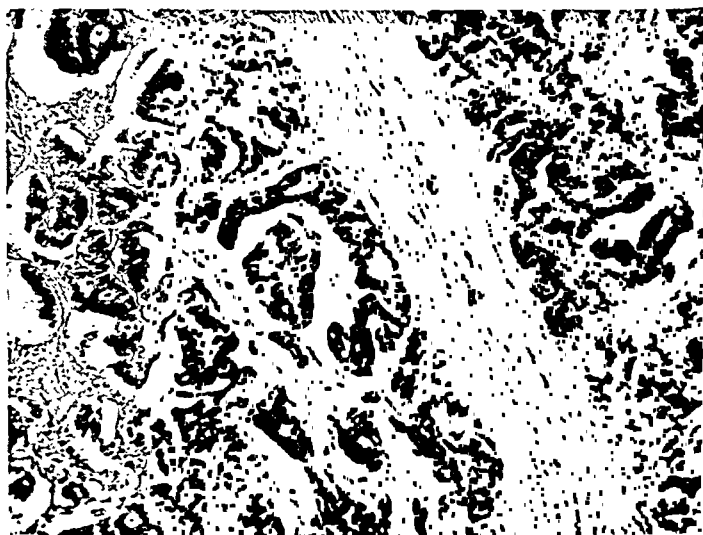


Fig. 2.—Typical adenocarcinoma of the colon discovered nine and one-half years after a primary malignant tumor of the uterine cervix.

On Jan. 29, 1940, with the patient under ether anesthesia, an exploration was made which disclosed the sigmoid and rectum densely adherent to the surrounding structures. A hard mass approximately 6 cm. in length was present about the

"*Sections.*—The section of right ovarian cyst showed an outer zone of normal ovarian stroma. Scattered through this were several small cysts lined with granular cells. The lining of the cyst was made up of pink-staining fibrous tissue and a broken layer of low cuboidal epithelium.

"The tube showed normal folds of mucosa with no inflammatory infiltration.

"*Diagnosis.*—Epidermoid carcinoma cervix uteri (gross). Normal tube, right. Simple serous cystoma ovary, right, benign. Normal tube and ovary, left (gross). (Note by Dr. Hugh Warren.)

"This was one of the few cases in which we had no microscopic examination. The specimen was such a beautiful one that it was preserved intact for museum purposes. There was no doubt of the character of the growth, as shown by its speedy return.

"In December, 1930, the patient began to have a watery discharge which continued and became very fetid. She had been running a temperature of 99.2° F. and sometimes 100° F., in the evenings.

"When I saw her on March 10, 1931, the vaginal vault was filled with a new growth, fully 8 cm. in diameter. There was also a small, friable growth in the right vaginal vault.

"The patient was referred to Dr. Curtis F. Burnam for irradiation."

We extracted the following from Dr. Burnam's communication:

"My first treatment was on March 11, 1931, when I introduced eighteen removable gold tubes into the growth, and gave a total dosage of 2.495 Gm. hours. On March 15, 1931, I used four removable tubes, which were left in for two hours; the total dose on that date was 0.7536 Gm. hours, or 753.6 mg. hours. On April 8, I used a plaque in the vault of the vagina, containing 1694 mc., for eighteen minutes. This amounted to a gram half hour.

"On April 9, 10, and 11, the patient was given x-ray treatment. The factors used were a distance of 57 cm., 1 mm. aluminum plus 1 mm. copper and several millimeters of sponge rubber, and I used a technique which I have rarely indulged in since. On April 9, I gave 800 roentgens over the abdomen, through a single portal, 7 by 7 cm. On the tenth, new areas of skin were taken and a similar dosage given to two areas. On April 11, two posterior portals were used with the same dosage. The total amount was 4,800 roentgens on the skin.

"In addition, on April 11, I gave 1 Gm. half hour of radium by a permanent implant into the left parametrium. On May 6 and 7, x-ray was again given.

"The patient cleared up very nicely. So far as I could make out, the local growth disappeared completely."

There never were any symptoms or signs of bowel irritability nor postirradiation proctitis.

She remained well in the interval of eight and one-half years until about the first of December, 1939, when she became unusually constipated. Laxatives provoked a diarrhea and abdominal cramps. These symptoms subsided in a few days and were succeeded by vague abdominal discomfort with distention but without vomiting. On Dec. 13, 1939, the patient was awakened by a sharp pain in the right upper abdominal quadrant. This was followed by the passage of a large amount of bright red blood from the rectum. The bleeding continued at such an alarming rate that she was admitted to The Western Pennsylvania Hospital the same day.

Upon admission the patient was a normal, obese, white woman except for a slightly distended abdomen and hyperactive peristalsis. Laboratory findings were not abnormal. She was given fluids parenterally, later by mouth, and oil retention enemas. Within forty-eight hours the bowels moved, and there was no further bleeding.

A roentgenogram of the colon showed a point of obstruction at the junction of the descending colon and sigmoid (Fig. 1, B). There was distention of the sigmoid and rectum, but no barium passed beyond the narrowing. There was no channel typical of a new growth and the obstruction was interpreted as an inflammatory stricture due to surrounding adhesions. A metallic foreign body resembling a radon seed was adjacent to the obstruction (Fig. 1, A).

FIBROMYOMA OF UTERINE CERVIX, PEDUNCULATED AND EXPELLED FROM VAGINA

RICHARD TORPIN, M.D., AND B. C. BEARD, M.D., AUGUSTA, GA.

(From the Department of Obstetrics and Gynecology, University of Georgia School of Medicine)

E S., negress, aged 29 years, slender constitutional type, poorly nourished, entered the hospital complaining of pain due to a grapefruit-size mass hanging from her vagina. She stated that thirty hours previously she was sitting on a slop jar and had two or three hard pains, rather like labor pains, and felt something slip down between her legs. She tried to push it back, but was not successful (Fig. 1). She had been sick for about three weeks in and out of bed suffering with pelvic pain, some nausea and vomiting, and a profuse vaginal discharge. A midwife treated her with tablets and douches. She states that she had noticed a "knot" in her lower abdomen for three or four months; and for the past three months had not been able to have sexual intercourse because of a mass filling her vagina.

For three or four months her bowel movements have been regular, but when she urinated only a small amount of urine was expelled, leaving a feeling of more in her bladder; but after the tumor was expelled and later excised, her urine flowed freely. Her last menstrual period was a few days late but of normal duration and flow. Previous periods were normal. She gave a history of first menstruating at twelve or thirteen years of age, always regular and of five or six days' duration; moderate flow and there was no change even during the last few months. She married at the age of 13 or 14 and has one child 13 years old. She stated that she had had 3 miscarriages at two to four months each, the last one being about one year ago.

The physical examination revealed otherwise essentially normal findings in a malnourished negress with subnormal mentality; temperature 100° F.; pulse, 110; respiration, 20. Her blood pressure was 130/70; her red blood cell count 4,000,000; hemoglobin 10 Gm. per 100 c.c.; white cell count 16,000 with 50 per cent polymorphonuclear leucocytes and 50 per cent lymphocytes. The urine had a small amount of albumin, but a clean specimen was difficult to obtain because of the mass protruding from her vagina.

The operation was performed with the patient anesthetized by cyclopropane inhalation. Because of a rather small pedicle the size of a large thumb attached to the lower edge of the posterior wall of the cervix, the diagnosis of a tumor rather than an inverted uterus was evident. The cervical canal, which was anterior to the pedicle, was dilated enough to admit a small finger, and when the protruding mass was pulled down, the cervix appeared at the introitus. The fundus uteri was enlarged and boggy, the size of a lemon, and it was freely movable and there were no lateral masses. The cervix was not elongated; thus the expulsion of the tumor from the vagina prolapsed the cervix and fundus to the introitus. Previously the uterus most certainly must have been elevated in the abdominal cavity nearly to the umbilicus. The pedicle was clamped and the mass excised. The clamp was then replaced by hemostatic ligatures. She made a rapid recovery without appreciable elevation in body temperature.

The gross pathology consisted of a fetal head-sized mass somewhat encapsulated but with a surface slightly irregular and necrotic in places. The consistency was homogeneous and indefinitely cystic feeling.

The mass measured 15 by 12 by 8 cm. and weighed 745 Gm. The cut surface was that of an edematous fibromyoma with a few small irregular cystic areas filled with serous transudate.

junction of the descending colon and the sigmoid. With difficulty the sigmoid was separated and resection of a typical carcinomatous mass accomplished. Two centimeters distal to the neoplasm, a benign stricture about 1 cm. in diameter was present. This was not apparent until the intestine was opened. It seemed to involve only the mucosal and muscular layers with a bandlike annular constriction. Anterior to this was found a radon seed which was the foreign body seen in the roentgenogram. There was no evidence of neoplasm in the pelvic organs nor metastases in abdominal lymph glands or liver. It was impossible to remove the stricture because sufficient bowel could not be freed.

The pathologic specimen consisted of large bowel 6 cm. long. The major portion of it was occupied by a firm mass with a craterlike ulcerated depression from the mucosal surface $3\frac{1}{2}$ cm. in diameter and $1\frac{1}{2}$ cm. in thickness. The serosal fat was hemorrhagic. Longitudinal section through the specimen exhibited infiltrating, grayish white, translucent tissue. The microscopic diagnosis was "adenocarcinoma, poorly differentiated with tumor extending to subserosal fat" (Fig. 2).

A smooth postoperative course was interrupted by a urinary tract infection, phlebitis of the right leg, and a partial disruption of the wound due to severe coughing. She was discharged two and one-half months following operation, and at the present time (July 1, 1940), six months after operation, she has gained in weight and is having no symptoms.

COMMENT

In a fairly extensive search of the literature we could not find a similar case. The benign stricture was typical of those due to irradiation and was probably the result of a combination of radium and roentgen therapy, although the amount certainly was not excessive. There had been no immediate intestinal reaction following irradiation and the stricture was not clinically significant until she developed signs and symptoms of colonic malignancy. Although bleeding from telangiectases has been reported³ as the chief complaint in some cases of stricture, a nine-year interval without bleeding made this possibility less likely and suggested new growth rather than stricture. The rarity of finding a benign stricture and a malignant growth simultaneously precluded the possibility of diagnosing both conditions before operation.

The attack of amebic dysentery suffered twenty-two years previously plus the radical panhysterectomy might have been contributing factors in the development of the benign stricture, in that adhesions held the bowel fixed in one position so that it received a maximum exposure of irradiation. The possibility of amebic dysentery producing an isolated stricture was considered remote. Multiple healed ulcers rather than stricture would have been expected. The carcinomatous area was situated directly above the stricture so that stasis might also have been one of the local inciting factors for the development of the neoplastic change in a cancer-susceptible individual.

In our opinion, the carcinoma of the bowel was a second primary tumor. The chance of this being a late metastasis is unlikely because of the typical microscopic appearance of adenocarcinoma of the colon without evidence of invasion from the outside. The recurrent malignant primary tumor of the uterine cervix for which the patient was treated nine years ago remains cured, according to our present standards for the evaluation of such data.

SUMMARY

Both a benign postirradiation stricture and primary adenocarcinoma of the proximal sigmoid colon were found nine years following successful radiation therapy for a recurrent malignant lesion of the uterine cervix.

REFERENCES

- (1) Collins, E. N., and Jones, T. E.: Surg. Gynec. Obst. 59: 644, 1934.
- (2) Corscaden, J. A., Kasabach, H. H., and Lenz, M.: Am. J. Roentgenol. 39: 871, 1938.
- (3) Jones, T. E.: J. A. M. A. 103: 1678, 1934.

or more; and in the ones of Counseller, Collins and Reel extended downward into the vagina through a well dilated cervical canal. In Reel's case the tumor in a white girl, 25 years old, weighed 7 kg.

Type B, interstitially growing tumor, is illustrated by Hall's case in which the tumor presented at the vulva, separating the labia more than two inches. The patient was a white woman 44 years old, the mother of 9 children, the youngest 11 years old. She had symptoms of pelvic distress, hypermenorrhea, and an acute attack of urinary retention. This tumor, probably as large as an orange, apparently arose from the posterior wall of the cervix and dissected interstitially between the posterior vaginal wall and the rectum and presented at the introitus of the vagina. It was quite bloodlessly enucleated through an incision in the vaginal wall covering it.

Type C, pedunculated cervical tumor within or protruding from the vagina, is well illustrated by the cases of Counseller, Cox, Church and Paterson, Christopher, von Zur-Mühlen and ours. All of these reports are accompanied by illustrations and each tumor developed entirely intravaginally and was pedunculated to the cervix. The patients, apparently all Caucasian, except ours, were aged 46, 37, 48, and 29. In general the effect on the uterine bleeding at menstruation was not marked in this class, but there was more or less urinary disturbance and in two cases the tumor specifically interfered with sexual intercourse. In two of the cases the tumor body was expelled from the vagina. In three of the cases the tumors were attached to the posterior lip of the cervix and in the other to the right lateral wall. One had operative treatment by abdominal total hysterectomy, the other three by vaginal extirpation of the tumor. All recovered. The pictures illustrating Christopher's, von Zur-Mühlen's, and our cases could be substituted for one another without loss of accuracy.

Type D, arising from a remnant of cervix, is illustrated by cases reported by Fletcher, Moench and Greenhill's second case. All of these apparently were in white women, aged 35, 42, and 43, and the time interval between operation of supracervical hysterectomy and the treatment of the tumor in the cervical stump was eight years, one year or so, and seventeen years. The weights of these tumors were 12½ pounds, 660 Gm., and about 2 pounds, respectively.

REFERENCES

- (1) *Caruso, P.*: AM. J. OBST. & GYN. 33: 696, 1937. (2) *Greenhill, J. P.*: Ibid. 31: 678, 1936. (3) *Counseller, V. S., and Collins, D. C.*: Ibid. 30: 108, 1935. (4) *Fletcher, H. N.*: Brit. M. J. 1: 300, 1935. (5) *Cattell, R. B.*: S. Clin. North America 13: 707, 1933. (6) *Counseller, V. S., Cox, F. W., Church, G. T., and Paterson, S. J.*: Ibid. 13: 966, 1933. (7) *Reel, P. J.*: AM. J. OBST. & GYN. 14: 386, 1927. (8) *Moench, L. M.*: M. Clin. North America 12: 1584, 1929. (9) *Christopher, F.*: AM. J. OBST. & GYN. 11: 668, 1926. (10) *Greenhill, J. P.*: Ibid. 19: 860, 1930. (11) *von Zur-Mühlen, F.*: Zentralbl. f. Gynäk. 51: 2483, 1927.

Todd, T. F.: Relief of Intractable Pain in Carcinoma of the Cervix Uteri, *Lancet* 2: 1305, 1939.

The author reports upon the relief of intractable pain in 84 cases of cervical carcinoma, 3 cases of rectal carcinoma, and 1 of prostatic carcinoma. These are subdivided in 2 types: visceral pain in 42 and somatic pain in 46 cases. Intractability can only be determined after a period of hospital observation and such an assay of the amount of pain should be made before operative relief is attempted. In visceral pain presacral neurectomy gave relief in all but one case. In somatic pain the author recommends intrathecal injection of absolute alcohol. There were four failures in this group. In addition to correct positioning of the patient, the most important points in the alcohol injection are to inject no faster than 0.5 c.c. in two minutes and not to inject more than 1 c.c. on any one occasion.

CARL P. HUBER.

The pathologic report stated that "most of the surface is ulcerated and inflamed, but in a few areas it is covered by stratified mucous epithelium. At one end there is a raw area 4 cm. in diameter."

Fibromas or fibromyomas of the uterine cervix obviously may be classified into several types: (a) those that arise in the upper part of the cervix and grow upward into the abdominal cavity, elevating the fundus above it; (b) those that arise in the middle portion of the cervix and extend out into the interstitial tissues of the lower broad ligaments laterally; under the urinary bladder anteriorly, or into the tissue between the peritoneum and vaginal mucosa posteriorly; (c) those that grow from the vaginal portion of the cervix and spend their entire existence within the vaginal cavity or protruding from it; (d) those that arise in the cervical stump remaining after supracervical hysterectomy operation.



Fig. 1.

According to Counsellor and Collins, Turunen in 1930 adequately reviewed the literature and collected 112 cases of cervical fibroma or fibromyoma and that 40 of these were encountered in pregnancy when the tumor either blocked or rendered childbirth exceedingly difficult. We find that there have been records of a dozen or more since that time. It might be of interest to review all cases and place them in the above classification. However that has not been done but some of the recent instances may be so presented.

Type A tumor arising from the upper portion of cervix elevating the fundus above it, is illustrated by Greenhill's first and third cases and by Counsellor and Collins' case and by Reel's case. These four instances, apparently all in white women, aged 42, 34, 49, and 25 years, respectively, had tumors in the lower part of the abdominal cavity and in the pelvis elevating the fundus in each case to or above the umbilicus. These tumors were all large, weighing 4 pounds each,

Several blocks of tissue were selected for microscopic study from representative areas, four of which are outlined in Fig. 2. Area 1 included the junction of the tumor and placenta (Fig. 3). Area 2 was angiomatous in structure (Fig. 4) while



Fig. 1.—Case 1. Placenta and tumor viewed from the fetal surface. Note the large, lobulated, protruding tumor mass.

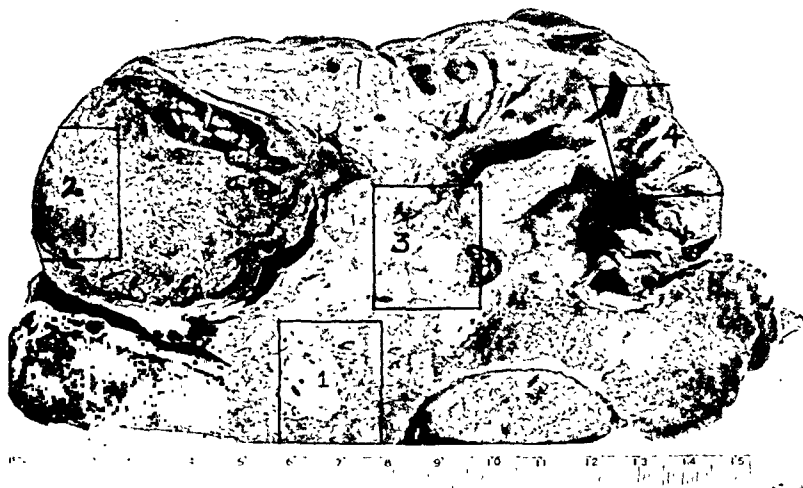


Fig. 2.—Case 1. Cut surface of vertical section through tumor and placenta at right angles to fetal surface, showing compact fibrous areas, spongy angiomatous areas, and several "blood cysts." Sections were taken from the outlined areas.

Area 3 was chiefly fibrous in character. Area 4 presented a combined fibrous and angiomatous composition containing several endothelial-lined "blood cysts." The angiomatous areas consisted of countless endothelial-lined spaces, dilated, and

CHORIOANGIOMA OF THE PLACENTA

JOHN H. FISHER, M.D., M.Sc., LONDON, ONT., CANADA

(From the Department of Pathology and Bacteriology, University of
Western Ontario Medical School)

CHORIOANGIOMA of the placenta is a benign tumor arising from chorionic mesenchyme and appears to be comparatively rare. Most of the papers on the subject contain reports of only single cases. It is barely mentioned in most of the accepted textbooks on obstetrics and gynecology, in part no doubt, because it seems to be of little definite clinical significance but perhaps because it has been largely overlooked.

Marchetti, in a very comprehensive article, has completely reviewed the literature up to 1939 in which he found 209 apparently authentic cases of chorioangioma of the placenta and added 8 cases of his own. However, it appears that he has overlooked a case reported by Rhamy. Subsequent to Marchetti's article a paper by Kotz and Kaufman and one by Siegel and Holley have appeared in the American literature, each recording a case of chorioangioma of the placenta. Kotz and Kaufman have reviewed the literature between 1924 and 1938 and pointed out that only 46 cases have been reported in that fourteen-year period.

The object of this paper is to record briefly two additional cases of chorioangioma of the placenta, including the gross and microscopic features of the placental tumors.

CASE REPORTS

CASE 1.—Mrs. T., white, gravida iv, aged 28 years, had had 3 normal pregnancies previously and the three children are living and well. The antenatal course in this fourth pregnancy was uneventful, although she admitted having attempted to produce an abortion by inserting some sort of wire stilette into her cervix which produced a little vaginal bleeding. No untoward effects developed and the pregnancy progressed. A normal full-term infant was delivered spontaneously by breech presentation on Feb. 2, 1939. There was no hydramnios and no excessive blood loss. The mother's blood serum was negative for syphilis. Before the placenta was expressed intact by the Credé technique, it was noticed that the uterus was unusually large and presented a peculiar heart-shaped form, so much so that the possibility of a twin pregnancy was suggested. The puerperium was essentially normal, although at one time it appeared that she was developing a femoral phlebitis. The attending physician sent the placenta to me for examination because of its peculiar shape and the presence of a large tumor-like mass distorting the amniotic surface.

Description of Placenta and Tumor.—The placenta was discoid in shape, weighed 1,150 Gm., and measured 17 cm. in its greatest diameter. The umbilical cord was eccentrically attached, lying at the margin of the tumor. The maternal surface was intact and free from gross changes except for three small infarcts. The fetal surface presented a large, lobulated tumor mass, measuring 14 by 11 by 7.5 cm. and protruding 5.5 cm. above the general fetal surface. The tumor was dusky, purplish red in color, semifluctuant in consistency and covered with smooth, intact but greatly stretched and elevated amnion. On cross section of the tumor in a vertical plane at right angles to the fetal surface of the placenta, the cut surface showed a rather variegated structure, partly solid and partly spongy and cystic. The compact gray areas appeared fibrous in structure, the spongy areas proved to be angiomatous in nature and the pseudocysts were filled with dark blood. The tumor was obviously arising from chorionic tissue from which it was quite well demarcated. The main gross features of the tumor are shown in Figs. 1 and 2.

some points, was heaped up into little syncytial masses. The cystlike spaces contained blood, and occasional focal calcareous deposits were present in the walls of the cysts. Sections of the placenta proper did not appear abnormal.

CASE 2.—Mrs. P. M., white, gravida i, aged 21 years. The last menstrual period was on July 10, 1936, the expected date of confinement April 17, 1937. The antenatal course was normal up to the sixth month, at which time the blood pressure was slightly raised to 142/94. At the seventh month the blood pressure was 158/104, the urine contained albumin 2+, and hydramnios was noted. At seven and one-half months the blood pressure was 164/116. X-ray picture showed an abnormal fetus and medical induction was employed. The membranes were

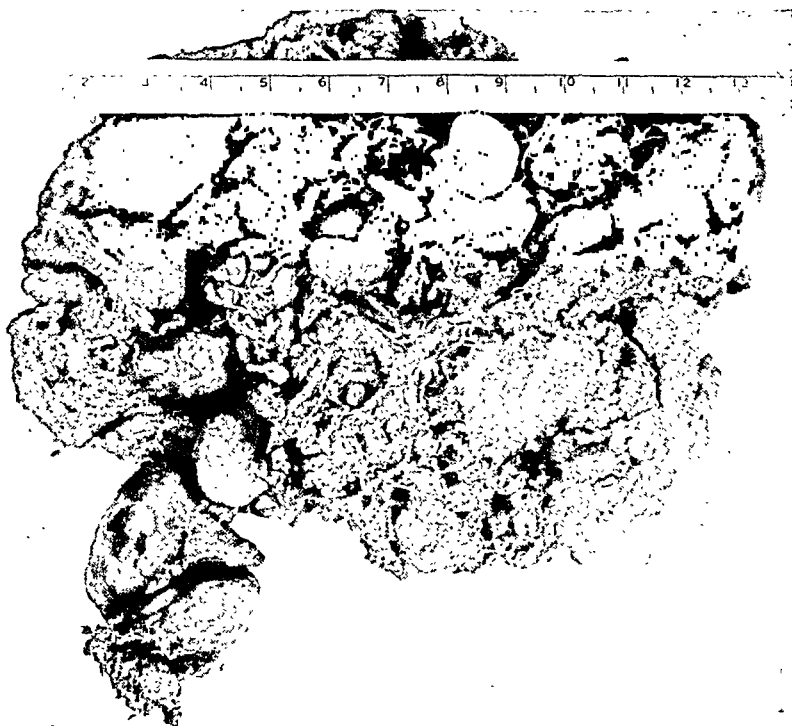


Fig. 5.—Case 2. Placenta and multiple chorioangiomas viewed from the maternal surface. Twenty or more pedunculated tumors of various sizes are attached to the chorionic villi.

artificially ruptured and delivery was spontaneous and easy. The infant was an approximately seven and one-half months stillborn, female, anencephalic monster with complete spina bifida. The placenta was delivered intact by the Credé technique. Blood loss was slight and the puerperium was normal. This patient subsequently delivered a normal, full-term infant in another city about Aug. 1, 1938, after a normal antenatal course.

Placenta.—The placenta was of normal size, measuring 17 by 16 by 3.5 cm. Its fetal surface showed nothing unusual. The umbilical cord was attached eccentrically. The maternal surface presented 25 pedunculated tumors attached to the chorionic villi by delicate, vascular stalks. The tumors were slightly mottled, reddish gray in color and varied in size from a walnut (3 by 2.5 by 2.5 cm.) to a millet seed (1 to 2 mm.). They hung down from the maternal surface attached by delicate stalks much like small red tubers or potatoes. Some of them lay partially or completely buried between cotyledons or villi. They were most numerous in the central part of the maternal surface. About 20 of the tumors may be seen in Fig. 5. Their cut surface presented a color and consistence like kidney tissue. Otherwise, the placenta showed nothing remarkable.

filled with blood. These capillary blood channels were separated by thin strands of dark-staining fibroblasts (Fig. 4). Some of the fibrous areas were composed of compactly arranged, adult collagenous fibers, while in others the structure resembled loosely arranged, embryonal mesenchymal cells, producing a myxomatous-like tissue. In these latter areas and also in the stroma of the angiomatous areas,

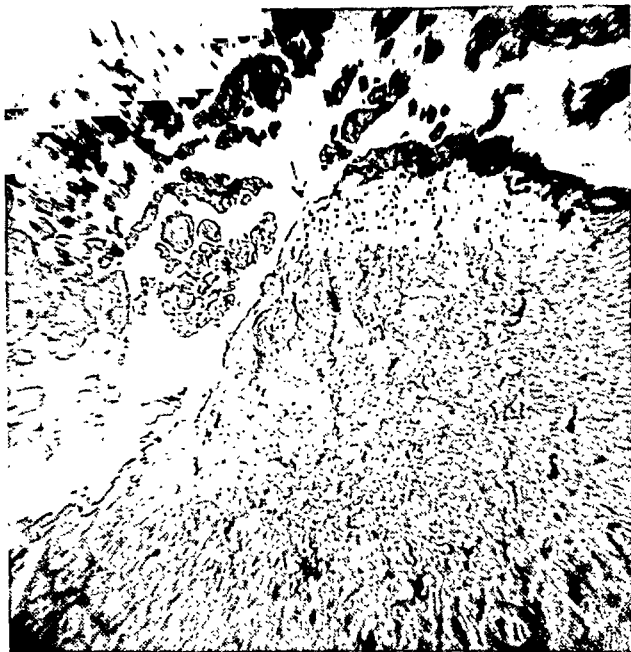


Fig. 3.—Case 1. Photomicrograph of junction between tumor and placenta. Area 1 outlined in Fig. 2. A single layer of syncytium (arrow) covers the tumor. $\times 36$.

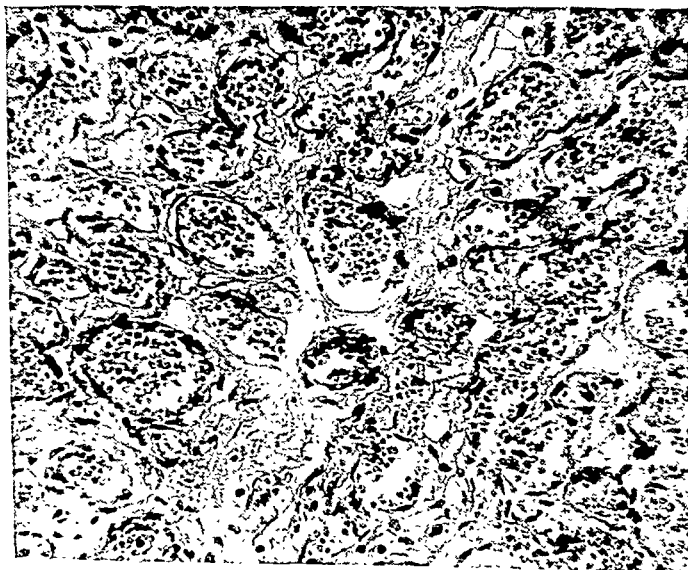


Fig. 4.—Case 1. Photomicrograph of Area 2, Fig. 2, showing angiomatous structure of tumor. $\times 230$.

there were found quite numerous, rather large mononuclear cells with fairly abundant, acidophilic cytoplasm, perhaps some sort of primitive blood cell. Incidentally, no erythroblasts or other evidence of erythroblastosis were detected in the chorionic villi. The "blood cysts" were lined with endothelium which, at

Case 1 was inclined to think that the large placental tumor accounted for the breech presentation, but it is more likely that the association was merely coincidental.

SUMMARY

1. Two cases of chorioangioma of the placenta are reported, including the gross and microscopic features of the tumors.
2. In one case the tumor was solitary but exceptionally large. In the other case the tumors were multiple and pedunculated.
3. In one case there was an associated hydramnios and a stillborn abnormal infant.
4. Retained placenta and post-partum hemorrhage were not encountered in either case.
5. A diligent search for chorioangioma of the placenta would probably show a higher incidence of this tumor than at present reported, as undoubtedly some instances have been overlooked in the past.

The author is greatly indebted to Dr. J. L. Duffy for the clinical notes and for permission to publish Case 1 and to Dr. Evan Shute for Case 2.

REFERENCES

- (1) Kotz, Jacob, and Kaufman, Morton S.: *M. Ann. Dist. Columbia* 8: 106, 1939.
- (2) Marchetti, Andrew A.: *Surg. Gynec. Obst.* 68: 733, 1939. (3) Rhamy, B. H.: *J. Lab. & Clin. Med.* 22: 899, 1937. (4) Siegel, Louis A., and Holley, Emerson: *Am. J. Obst. & Gynec.* 38: 353, 1939.

PRIMARY DIFFUSE ADENOCARCINOMA OF THE VAGINA*

MONTE C. PIPER, M.D., ROCHESTER, MINN.

(From the Section on Obstetrics and Gynecology, the Mayo Clinic)

TWO cases of primary diffuse adenocarcinoma of the vagina have been observed in the Mayo Clinic within two years. The first case was reported by Scannell in 1939, who credited Broders with the tissue diagnosis. The second case is reported herewith and some features which were observed in both cases of this apparently rare condition will be mentioned.

An instance of diffuse adenosis of the vagina was reported by Bonney and Glendinning in 1911, and they referred to a report of a similar condition by Prueschen in 1877. In neither of those cases had malignant change taken place but active glands secreting mucinous fluid were present.

REPORT OF CASE

In February, 1940, a white woman, aged 29 years, consulted the gynecologic department because of menstrual irregularity, intermenstrual pelvic pain of two and one-half years' duration and intermenstrual spotting. The patient had had scarlatina at the age of 5 years, had undergone appendectomy when she was 17 years of age, had "dry pleurisy" at the age of 18 years, and had been subjected to tonsillectomy at 20 years of age. Two anal operations had been performed, one at the age of 27 and the other at the age of 28 years.

The dermatologic history was interesting. Lichen planus had appeared about the ankles at the age of 21 years and eventually had involved most of the bodily surfaces except the face. Specimens of skin taken from the back for biopsy had confirmed the diagnosis. At the age of 22 years, in 1932, when the patient first had visited the clinic because of the cutaneous condition, the lesions had involved

*Presented at a meeting of the North Dakota State Society of Obstetrics and Gynecology, Minot, N. D., May 7, 1940.
Submitted for publication July 18, 1940.

Microscopic study showed that the tumors were partly covered with a membranelike layer of trophoblastic epithelium. They presented an angiomatous structure corresponding to the vascular or mature type of chorioangioma as described by Marchetti. They were composed of abundant blood vessels, chiefly of capillary caliber, closely packed together with little supporting stroma (Fig. 6). In some areas the fibrous connective tissue was more abundant but loosely arranged and rather immature-appearing. A small amount of old blood pigment was present in the stroma both lying free and contained within large phagocytic cells. Sections of the placenta itself appeared essentially normal.

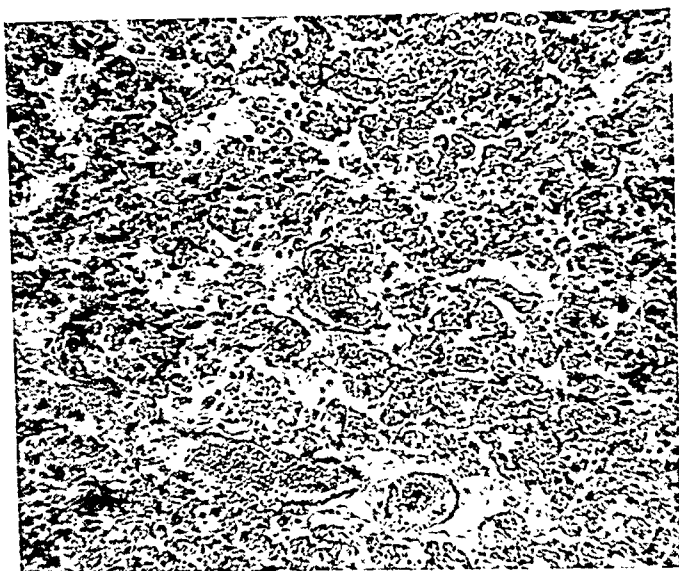


Fig. 6.—Case 2. A typical angiomatous area. $\times 100$.

COMMENT

In both cases here reported, the chorioangiomas show some unusual features. In Case 1, the tumor was exceptionally large. Few larger ones have been reported. The placenta as a whole, including the tumor, was approximately 550 to 600 Gm. above normal weight. The tumor was situated in the more common location, on the fetal surface. The question was raised in Case 1 as to whether or not the patient's attempt to produce an abortion might have acted as an etiologic factor in the production of the tumor, but this seems highly improbable. Syphilis, mentioned by some writers as an etiologic factor, exerted no influence in these two cases.

Case 2 is unusual in that the tumors were multiple and numerous. In most instances, the tumor is single, although the number in any one placenta may be as high as 100. The tumors were attached to the maternal surface of the placenta in Case 2. While this is a less common location than the fetal surface, it is not particularly uncommon.

Opinions differ widely concerning the clinical significance of chorioangioma of the placenta. Kotz and Kaufman state that, in their opinion, there is a definite correlation between chorioangioma and hydramnios, premature labor, stillbirth, and post-partum hemorrhage. Marchetti, on the other hand, feels that, with possible rare exceptions, chorioangioma possesses no clinical significance. Analyzing the 2 cases which I am reporting, it is found that hydramnios was present in Case 2 but not in Case 1. Premature labor occurred in Case 2, but it was artificially induced, while in Case 1 the pregnancy went to term and labor onset was spontaneous. Case 1 produced a normal, living, full-term infant, while the infant in Case 2 was a stillborn, anencephalic monster with spina bifida. No post-partum hemorrhage was encountered in either case. The attending physician in

when some projecting tissue on the right of the orifice was pushed farther to the right. This projecting tissue protruded 1 cm. and was attached to the right of the meatus by a parallel base, 1 cm. long and less than half that broad. This peculiar tissue seemed bluntly pointed at times and again slightly more lobulated, as though it were collapsed or less dense. It was suggestive of erectile tissue. There was no such formation on the left of the meatus. It did not appear to be an ordinary caruncle or as prolapsed urethral tissue. A serosanguineous fluid, slightly blood stained, exuded from the vagina, and the orifice was too sensitive to permit examination by more than one finger. The anterior vaginal wall was

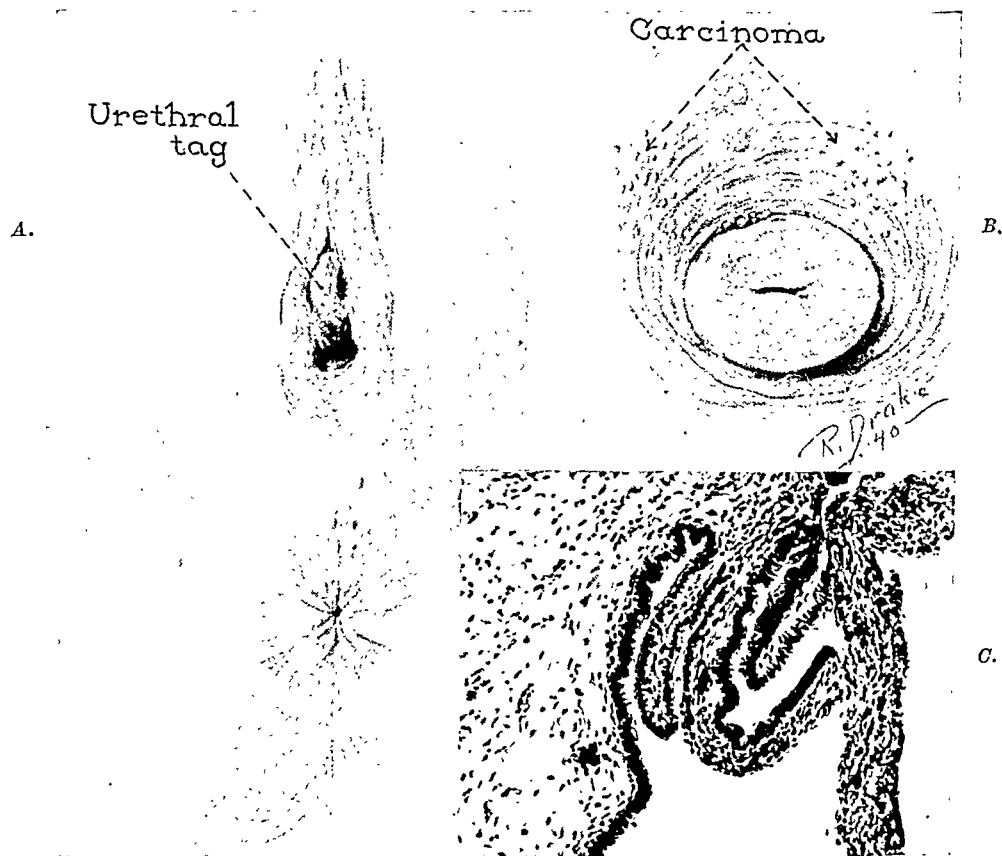


Fig. 1.—A, Abnormalities of external genitalia; B, nodular projections in anterior vaginal wall; C, papillary adenocarcinoma, Grade I.

short, the cervix was anterior and the medium-sized fundus had undergone retroversion, Grade 3. The adnexa seemed normal to palpation. The vaginal wall, each side of the vault and in the anterior cul-de-sac, felt strangely granular (Fig. 1, B). Along either side of the vaginal portion of the urethra was a fibrous strip in which were nodular projections that felt like small submucosal fibromas. They were rounded, firm, and smooth and the largest was about 3 mm. in diameter. One of these was on the left; three were in a row on the right and seemed to connect with the perimeatal projection mentioned before. With the aid of a local anesthetic and a small speculum, the vaginal walls were brought into view. In either lateral vault and over the portio vaginalis in the anterior cul-de-sac were fine, glistening projections, as though grains of sand were beneath the epithelium. Some refracted light as though they were small, mucinous cysts, and others were darker red than the color of the surrounding surface. Twelve of these were counted on the right and nearly as many on the left, while perhaps eight were seen over the portio vaginalis. The periurethral nodules in

the external genitalia and had been described as purplish, flat, shiny, angular areas scattered all over the genitalia. Also, at this time there were lesions in the mouth consisting of firm, whitish material about the dentate margins; a biopsy of the mucous membrane revealed filaments resembling mycelia, suggestive of thrush. However, a positive culture of significant fungi was not obtained. When the patient was 25 years of age, a dermatologist had recorded that the mucous membrane of the vagina resembled that of the mouth but the Wickham's stria seen in cases of lichen planus were absent. Also when the woman was 25 years of age, it was noted that an associated seborrheic dermatitis had resulted in areas of "alopecia cicatrisata" to which phenol had been applied. The conjunctivae of both eyes had been the site of superficial punctate keratitis, with small lesions near the limbus resembling subepithelial cysts. Various therapeutic agents had been employed; these had included, at first, ultraviolet light and subsequently mercury pills; Fowler's solution by mouth, sodium cacodylate hypodermically; local applications of formalin, acriflavine, and gentian violet solution; metaphen ointment to the conjunctivae, and a variety of vitamins. The condition of the mouth was somewhat alleviated following administration of the vitamins.

The metabolic history also was of interest. In 1934, the metabolic rates had been -3 and -5 per cent; this was at a time when the patient was taking estrogenic substance because of a menstrual irregularity, as will appear. Early in 1938, she said, readings of the metabolic rates had been -21 and -23 per cent. The history was somewhat suggestive of myxedema. Thereafter, for about a year, the woman had taken desiccated thyroid gland daily. For the year before her admission in 1940 she had continued to take desiccated thyroid gland but in a larger dose than before, namely, in doses of 3 gr. (0.2 Gm.) per day. This dose apparently lessened her fatigue and her tendency to gain weight. On admission, her metabolic rate was +3 per cent.

Menstruation had begun at the age of 10 years and had occurred every twenty-eight days until the age of 22 years, or about a year following onset of the lichen planus. Then menstruation had begun to increase in frequency. At the age of 24 years intermenstrual spotting had begun and had continued for more than a year. This was thought to be on the basis of ovarian dysfunction. Rectal examination then had given negative results except that it had disclosed the presence of a congenital type of uterine retroversion and estrogen had been administered, apparently with some good effect on the spotting. At the age of 27 years, midmenstrual cramps had appeared on the left side; sometimes these were rather severe and were accompanied by bleeding during the intermenstrual interval. Menstruation had become irregular and dribbling of menstrual material had continued for eight days after a normal two days of flow. This condition had been gradually progressive up to February, 1940. Dilatation and curettage had been performed elsewhere in February, 1938, and in August, 1939, and following the last of these operations a tentative diagnosis of endometriosis had been made.

The patient's mother had died of endocarditis at the age of 42 years and one sister had lichen planus.

The woman had an erect, well-proportioned figure, somewhat broad shoulders, a strong waist, not particularly prominent hips or breasts but no abnormal hirsutism. Her height was 5 feet, 6½ inches (169 cm.), her weight was 150 pounds (68 kg.), and she seemed alert and intelligent. There was an area of alopecia over the vertex of the scalp. Buccal mucous membranes were of a velvety, bluish red, and the skin revealed some residual evidences of lichen planus. Sensitivity over both lower abdominal quadrants was increased.

The external genitalia were hypoplastic or atrophic and revealed several abnormal manifestations (Fig. 1, A). The fissure of the vestibule was partly sealed from both sides, and there was no apparent evidence of clitoris or prepuce. The labia minora were small, shortened, and flaccid, and the introitus was atrophied, small, and hypersensitive. The urethral meatus was a vertical slit seen only

Physical examination was negative except for the pelvic findings. The uterus was enlarged, reaching 5 cm. above the symphysis, irregular in outline. A circumscribed nodular mass could be felt in the anterior uterine wall. Mobility was not diminished. There was no tenderness in the adnexal regions and no other masses could be felt.

Laboratory Data.—Red blood count 4,900,000. Hemoglobin 14 Gm. Red blood cells appeared normal. White count 7,600. Differential: polymorphonuclear leucocytes 71, lymphocytes 29. Sedimentation rate at the end of one hour 6 mm.

After a preliminary diagnostic curettage, a supravaginal hysterectomy was performed.

Pathologic Report.—The specimen consisted of a uterus, both tubes, and the left ovary. The tubes revealed some thickening at the fundal end and on section the wall was thickened and fibrosed. The ovary presented no abnormalities. The uterus measured 10 by 7 by 6 cm. and, bulging in the anterior wall, there was a

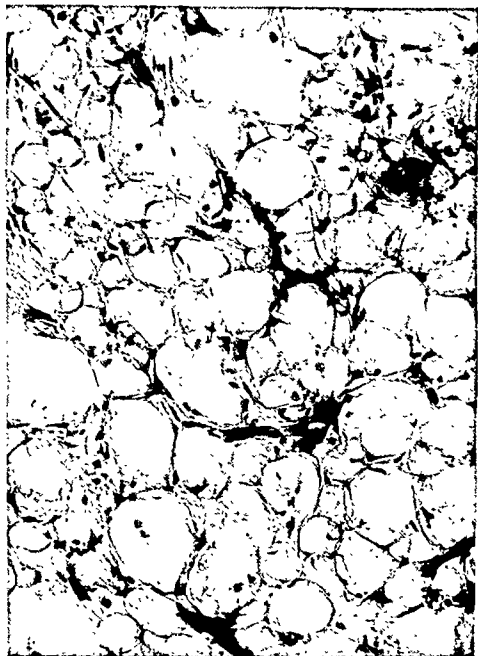


Fig. 1.—Hematoxylin-eosin stain. $\times 150$.

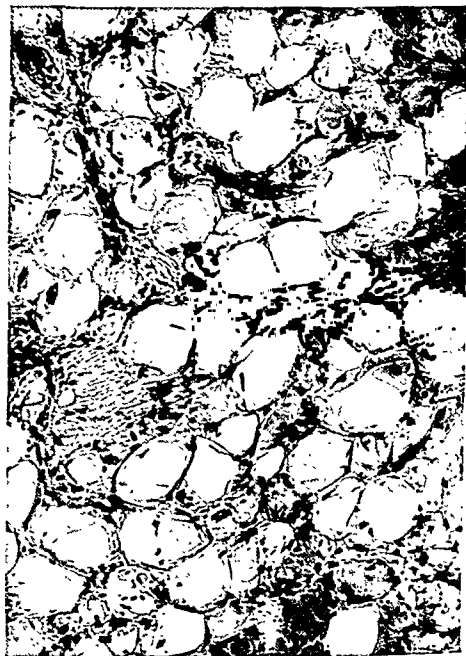


Fig. 2.—Scharlach R stain. $\times 150$.

discrete, circumscribed mass 7 cm. in diameter, which had a definite capsule of uterine tissue about it. The mass was lemon yellow in color and rubbery in consistency. On section the color was uniform throughout, making the tumor stand out from the surrounding normal uterine tissue. The cut surface had the same appearance throughout. No macroscopic blood vessels were visible. The tumor mass could easily be peeled from the adjacent tissue.

Two centimeters from the large tumor, toward the fundus, was a second mass 3 cm. in diameter. This was similarly discrete and encapsulated, but was pearly white throughout and contained no yellow areas. This latter mass had the characteristic whorl-like appearance of leiomyoma of the uterus. The cavity of the uterus was distorted by the large mass and the endometrium was 1 mm. thick.

Microscopic Examination.—The histologic picture of sections stained with hematoxylin-eosin (Fig. 1) revealed a uniform structure composed of large cells with the nucleus pushed toward the periphery. These cells apparently contained no protoplasmic material and were supported by a very thin connective tissue stroma. Nowhere in the sections were there any leiomyomatous elements. Sudan III and Scharlach R (Fig. 2) stains revealed that the vacuolated cells were artefacts due to fixation and the cells were distended with fat. An osmic acid preparation

the anterior vaginal wall had the more usual appearance of submucous fibromas. Several of the smaller projections from each lateral wall and over the cervix in the cul-de-sac were snipped out with a biopsy punch.

The pathologist reported papillary adenocarcinoma Grade 1 in all situations (Fig. 2). Subsequently specimens for biopsy were obtained from the projecting tissue at the side of the meatus as well as from the nodules to the right of the urethral tube, in the vagina. These were inflammatory tissue and when the slides were reviewed subsequently by the pathologist, the tissue was said to contain, in one area, a structure resembling the spaces observed in erectile type of tissue. A specimen from the endocervix proved to be only a blood clot. Surgical and radiologic consultation resulted in the administration of a total of 1,526 mg. hr. of radium given in four divided applications to the vaginal wall.

COMMENT

The unusual features of this case were the chronic ectodermal lesions and the abnormal basal metabolic variations. Whether the periurethral tissue may be an evidence of bisexualism is considered a possibility.

Features common to this case and to the case reported by Scannell are that the patients were approximately of the same age; the duration of symptoms was nearly the same; there were slight evidences of masculinity in bodily contour; the dermal structures were sensitive to mild irritation; there was a history of vaginal irritation of long duration, and adenocarcinomatous tissue of low grade of malignancy was diffusely spaced in the vaginal epithelium.

REFERENCES

- (1) Bonney, Victor, and Glendining, Bryden: *Proc. Roy. Soc. Med.* 4: 18, 1911.
- (2) von Preuschen: Quoted by Bonney, Victor and Glendining, Bryden.
- (3) Scannell, R. C.: *AM. J. OBST. & GYNEC.* 38: 331, 1939.

LIPOMA OF THE UTERUS

FRED L. RITTER, M.D., AND SYDNEY W. STRINGER, M.D.,
SYRACUSE, N. Y.

(From the Department of Gynecology, Syracuse University)

LIPOMA of the uterus is a rare neoplasm. In 1922, Petersen¹ reviewed the literature on mixed tumors and collected 31 cases. Of this group, only 10 were classified as simple lipomas. Of the remaining 21 cases, 14 were called fibromyolipomas, 5 as lipomatous areas in mixed tumors, and 2 as liposarcoma. Twenty-eight per cent of the mixed tumors reported were considered to be malignant, in that metastases were reported. He added one case in which 94 per cent of the tumor consisted of fatty areolar tissue. Thirteen additional cases have since been reported, one each, by Preissecker,² Starry,³ Dworzak,⁴ Bride,⁵ Engelhard,⁶ Lund,⁷ Muschik,⁸ Nordin,⁹ Burger,¹⁰ Glas,¹¹ Humphrey and Mustard,¹² and two by Thaler.¹³ One case, Humphrey and Mustard's,¹² was associated with carcinoma of the uterus, and one case, Engelhard,⁶ was reported as a malignant lipoma. In view of the rarity of these tumors, it seems worth while to report another case.

CASE REPORT

Mrs. E. D., aged 57 years, had had a yellowish, watery vaginal discharge, occasionally slightly tinged with blood, for six weeks, slight backache, and a bearing down sensation. Menses began at 12. She had had two normal pregnancies; menopause at 45, with very little discomfort. She had no symptoms referable to the pelvis until the onset of the present trouble. Her general health had always been excellent. There had been no loss of weight and no gastrointestinal or urinary tract disturbance.

VELAMENTOUS INSERTION OF THE UMBILICAL CORD

AS A CAUSE OF FETAL DEATH IN A TWIN PREGNANCY

J. W. RECORDS, M.D., OKLAHOMA CITY, OKLA.

(From the Obstetrics Department of Wesley Hospital and the Department of Obstetrics of the University of Oklahoma School of Medicine)

THE term velamentous insertion of the umbilical cord refers to the condition existing when the vessels of the cord separate at varying distances from the placenta and reach their place of insertion in the placenta by running between the amnion and the chorion. The theory of causation of the anomaly most generally accepted is that advanced by Franque, namely, that in such cases in early pregnancy the most vascular part of the ovum may be in the decidua capsularis instead of in the decidua basalis, in which case the abdominal pedicle takes its origin from the former tissue. However, with the advance of pregnancy the decidua basalis becomes the most vascular area, the abdominal pedicle retains its original position, the vessels extending from its maternal end to the margin of the placenta.

The anomaly has been found to occur in from 0.4 to 1.25 per cent of placentas by various observers. It occurs more frequently in multiple than in single pregnancies.

CASE REPORT

A 26-year-old white housewife was first seen for prenatal care Sept. 18, 1939. Her last menstrual period began on July 2, 1939, and was normal. There were no previous pregnancies. The family history and the past history were irrelevant. The pregnancy was without serious complications. The blood, Kline and Wassermann tests as well as periodic urinalyses were negative.

At various intervals the systolic blood pressure varied from 90 to 122 and the diastolic from 50 to 68. The total weight increase was from 94 pounds to 118 pounds.

The diagnosis of twin pregnancy was made and confirmed by x-ray in the thirty-second week of pregnancy. On March 22, 1940 (thirty-fourth week), the membranes ruptured without previous labor pains and a considerable quantity of bright blood accompanied the escaping amniotic fluid. The duration of the bloody show was very short and on admission to the hospital one hour later there was only a small amount of blood-tinged discharge.

The blood pressure was 110/60, and she was beginning to have slight uterine contractions every five minutes. The head of the lower fetus was engaged, the position being right occiput anterior. The position of the upper fetus was transverse with the head in the left upper quadrant. Fetal heart tones were heard over most of the right side of the abdomen, both above and below the level of the umbilicus.

The labor proceeded normally for about seven hours when an umbilical cord was seen to be prolapsed from the vagina. The patient was put on the delivery table immediately and an attempt was made to replace the cord. The cord was pulseless, flaccid and green in color, giving the impression that it had been functionless for some time. Vaginal examination disclosed that the cervix was about four fingers dilated, and protruding from the external os was an intact bag of waters. This was ruptured and a large amount of meconium-stained amniotic fluid escaped. A firm fetal head immediately settled into the cervix.

Fetal heart tones were easily heard in the right lower quadrant and in no other locations. Attempts at complete reposition of the umbilical cord were unsuccessful, and when the cord was held up between the head and the cervix, releasing the pressure, no pulsation occurred. The patient continued in labor, the cervical os completing its dilatation rapidly, and about two hours after the prolapsed cord was first seen the head was visible for an extent of about 8 cm. in diameter. Delivery of a living male infant was then effected with low forceps after a small medio-lateral episiotomy.

This infant's respiration was sluggish, and it required resuscitation with inhalations of oxygen and carbon dioxide mixture. Five minutes later a stillborn male infant was delivered spontaneously from right occiput anterior. This fetus obviously had been dead for several hours, its skin exhibiting a dark red discoloration and

revealed a slight, if any, staining of the fat granules. One section revealed that the capsule of the tumor was connective tissue from which there extended delicate strands making up the stroma of the mass.

A section through the smaller tumor revealed no fat cells and the typical structure of a leiomyoma of the uterus. The endometrium was proliferative in type with some evidence of cystic change.

DISCUSSION

The histogenesis of fatty tumors of the uterus has not, as yet, received definite interpretation. Von Franque¹⁴ views it as an example of metaplasia. Merkel¹⁵ believes they arise from displaced embryonic mesoderm. Knox¹⁶ considers them as supporting Conheim's theory of embryonic rests, which in developing, produce fatty tumors. Brunings¹⁷ belief coincides with that of Lockyer¹⁸ who expounds the premise that lipomas of the uterus are the result of the transformation of muscle bundles into fat. In addition, the Wolffian duct theory of Wilms and the growth of true fat along nerve and blood vessels from adjacent structures have been brought forward as possibilities of pathogenesis. Elkin and Hawthorn¹⁹ have reviewed carefully the various theories of histogenesis and conclude that the question involved is whether the tumor is composed of true fat cells arising from a lipoblast or whether some other type of cell such as connective tissue cells has undergone fatty infiltration. They favor the lipoblastic origin of these tumors. Meyer and Sydel²⁰ believe they arise from displaced embryonic mesoderm. Starry³ feels that they must represent either the type of connective tissue cells commonly found in the uterus or that they represent some specially differentiated type of lipogenic connective tissue cell. In reviewing these theories, it is noted that they form two groups, the question being whether lipomas of the uterus arise from a true fat cell, the lipoblast, or whether or not a metaplasia of a different type of cell occurs, it being infiltrated with fat globules and transformed into fat-bearing cells.

This instance of a fatty tumor of the uterus reveals a mass of fat-containing cells supported by connective tissue stroma and surrounded by a thin capsule of connective tissue and condensed uterine muscle. Nowhere in multiple sections of the primary tumor mass have there been discovered muscle, cartilage, or other tissue elements. All the cells are mature fat-containing units and nowhere can there be noted evidence of metaplasia or fatty degeneration. In direct contrast, the adjacent typical leiomyoma contains no fat-bearing cells or fatty change of any kind. The evidence presented is directed in favor of a true lipoma of the uterus.

REFERENCES

- (1) *Petersen, A. J.*: J. Lab. & Clin. Med. 8: 369, 1922.
- (2) *Preisseecker, E.*: Wien. Klin. Wchnschr. 39: 51, 1926.
- (3) *Starry, A. C.*: Surg. Gynec. Obst. 41: 642, 1925.
- (4) *Dworzak, E. H.*: Ztschr. f. Path. 34: 20, 1926.
- (5) *Bride, J. W.*: J. Obst. & Gynaec. Brit. Emp. 36: 83, 1929.
- (6) *Engelhard*: Nederl. tijdschr. v. geneesk. 1: 224, 1929.
- (7) *Lund, F. B.*: New England J. Med. 208: 536, 1933.
- (8) *Muschik, A.*: Ztschr. f. Geburtsh. u. Gynäk. 105: 444, 1933.
- (9) *Nordin, F.*: Hygiea (Festband) 100: 384, 1938.
- (10) *Burger, P.*: Gynécologie 37: 269, 1938.
- (11) *Glas, R.*: Zentralbl. f. Gynäk. 54: 514, 1930.
- (12) *Hymphrey, A., and Mustard, R. L.*: AM. J. OBST. & GYNEC. 36: 159, 1938.
- (13) *Thaler, H.*: Arch. f. Gynäk. 134: 350, 1928.
- (14) *Von Franque*: Verhandl. d. deutsch. gesellsch. f. Gynäk. 9: 491, 1901.
- (15) *Merkel, H.*: Beitr. z. path. Anat. u. z. allg. Path. 29: 274, 1903.
- (16) *Knox, J. H. M.*: Johns Hopkins Hosp. Bull. 12: 318, 1901.
- (17) *Brunings*: Verhandl. deutsch. Gesellsch. f. Gynäk. 8: 348, 1899.
- (18) *Lockyer*: Lewis, Practice of Surgery, Hagerstown, Md., W. F. Prior Co., Vol. XI.
- (19) *Elkin and Hawthorn*: Surg. Gynec. Obst. 25: 72, 1917.
- (20) *Meyer, R., and Sydel, O.*: Ztschr. f. Geburtsh. u. Gynäk. 50: 274, 1903.

PARALDEHYDE ANALGESIA AND PERINEAL ANESTHESIA IN OBSTETRICS*

C. K. FRASER, M.D., AND J. W. JONES, M.D., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, George Washington University School of Medicine, Washington, D. C., and the Department of Obstetrics and Gynecology, Duke University Hospital, Durham, N. C.)

THE purpose of this paper is to present our clinical observations based on personal experiences in the use of paraldehyde analgesia with perineal anesthesia in terminating the second stage of labor.

We have also incorporated a series with complications of pregnancy and parturition in which other forms of analgesia were employed, but the delivery was accomplished with perineal anesthesia.

The incentive for our interest in this field was derived from two sources. W. Z. Bradford demonstrated the technique and the value of perineal anesthesia in obstetrics. H. F. Kane suggested the application of this obstetric refinement in terminating labors in which paraldehyde, as an amnesiac, has been employed.

The practice of blocking the pudic nerve was first used in Germany by Ilmer¹ in 1910. In 1913 it was introduced into this country by Gellhorn,² although he later gave it up for local infiltration. A relatively small number of papers have since appeared in the literature on this subject. King³ in 1916 presented a very practical discussion on the anatomy of the female perineum and the technique of nerve block and infiltration. Torland,⁴ Greenhill,⁵ Bradford,⁶ Ruth and Stiles,⁷ Walker,⁸ Ditter,⁹ Urnes and Timerman,¹⁰ have contributed papers which point to the advantages of perineal anesthesia in certain cases. All report good results whether nerve block, local infiltration or a combination of these methods was used.

METHOD

We have used a combination of nerve block and local infiltration. The patient is prepared and draped for delivery. The pubic arch and ischial tuberosities are palpated for orientation. A point on the skin midway between the rectum and ischial tuberosity is selected for the entrance of the needle. King³ recommends spraying the site of puncture with ethyl chloride, others inject an intradermal wheal with a hypodermic needle. We have found their use unnecessary if the patient is under adequate analgesia.

If a perineotomy is to be done, the injection is made first on that side, for the action of the drug is more complete at the point of incision. A 22 gauge needle, 10 cm. in length, is inserted at the selected area and directed just medial to the ischial tuberosity.

With one finger in the vagina, the point of the needle is guided posterior to the ischial spine, care being taken not to pierce the vaginal wall. The needle is brought to rest proximally and posterior to the ischial spine. Traction is made on the plunger and if blood is not aspirated, 10 c.c. of a 1 per cent solution of procaine hydrochloride is injected. By withdrawing the needle 2 or 3 cm., some of the solution is deposited beneath Colles fascia where, as pointed out by King,³ the anatomic arrangement of the fascia does not allow the solution to escape save anteriorly where it will bathe the terminal branches of the pudendal nerve anterior to the triangular ligament. The

*Read, by invitation, at a meeting of the Washington Gynecological Society, March 23, 1940, Washington, D. C.

several large areas of maceration. The fetal head was extremely soft. No other abnormalities were noted. Three minutes later the placenta was expelled without difficulty. There was no abnormal bleeding.

The infant delivered first weighed 1,518 Gm. (4 pounds 5 ounces). The stillborn infant weighed 1,320 Gm. (3 pounds 12 ounces). The placenta weighed one kilogram and was 20 cm. in diameter. The cord to the living baby was 48 cm. in length and was inserted eccentrically about 6 cm. from the edge of the placenta.

The cord to the stillborn fetus was 54 cm. in length, about one-half the diameter of the other one and was attached to the edge of the membranes; the umbilical vessels running between the two layers of the membranes for a distance of 8 cm. before entering the placenta. At a point near the entrance of the vessels into the substance of the placenta on the maternal side were seen two breaks in the vessel walls with hemorrhage between the membranes.

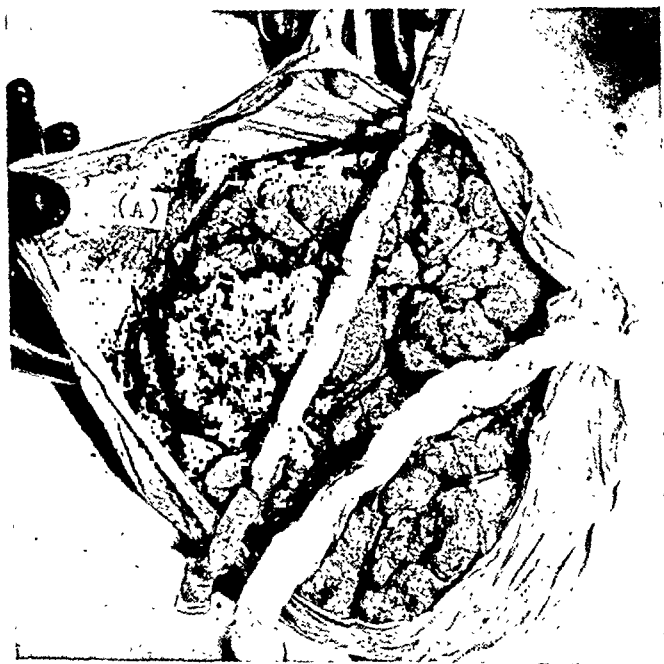


Fig. 1.—Maternal surface of placenta. Velamentous insertion of the cord (above) with point of rupture of umbilical vessels at A. Normal cord at right.

SUMMARY

A case is reported of velamentous insertion of the umbilical cord with rupture of the umbilical vessels, probably causing death of one fetus of twins in utero and onset of premature labor.

The possibility of fetal death resulting from rupture of the umbilical vessels in their course between the two layers of the membranes is illustrated by the case reported. The condition may be suspected when moderate bleeding and signs of fetal cardiac embarrassment or death appear at term with no evidence of placenta previa or premature separation of the normally implanted placenta.

REFERENCES

- Kosmak, G. W.: *AM. J. OBST. & GYNEC.* 16: 438, 1928. Boley, H. B.: *Ibid.* 25: 156, 1933. Whitehouse, A. J.: *Ibid.* 33: 527, 1937. Morehead, D. E., and De Carle, D. W.: *Proc. Staff Meet. Mayo Clin.* 6: 391, 1931. Arey, L. B.: *Curtis' Obstetrics and Gynecology*, Philadelphia, W. B. Saunders Company 1: p. 472. Schumann, E. A.: *Curtis' Obstetrics and Gynecology*, Philadelphia, W. B. Saunders Company 1: p. 506.

factory. In a few instances in which a deep perineotomy was utilized, there was some discomfort when the incision extended to the area supplied by the inferior hemorrhoidal and posterior cutaneous nerves of the thigh. In such cases the local infiltration may be augmented so as to include the posterior triangle as described by King.³

It will be noted that Table I includes uncomplicated cases, the majority of which are primiparas. All had paraldehyde analgesia. They were terminated with perineal anesthesia.

A series with complications of pregnancy and parturition is presented in Table II in which primiparas predominate. Other forms of analgesia were employed. All cases were terminated with combined nerve block and local infiltration.

TABLE I. PARALDEHYDE ANALGESIA

A. Parity:	
a. Primiparas	28 cases
b. Multiparas	3 cases
B. Position:	
a. Occipitoanterior	31 cases
C. Type of delivery:	
a. Perineal forceps and extraction	28 cases
b. Spontaneous parturition	3 cases
c. Perineotomy and repair	28 cases
d. Repair primary laceration	1 case

TABLE II. OTHER FORMS OF ANALGESIA

A. Parity:	
a. Primiparas	14 cases
b. Multiparas	6 cases
B. Position:	
a. Occipitoanterior	14 cases
b. Occipitotransverse	2 cases
c. Occipitoposterior	1 case
d. Right sacroanterior	3 cases
C. Complications of pregnancy and parturition:	
a. Eclampsia and active pulmonary tuberculosis	6 cases each
b. Arrested pulmonary tuberculosis, diabetes mellitus with acidosis and pre-eclamptic toxemia, lobar pneumonia, hypertension and cardiac failure, pre-eclamptic toxemia	1 case each
c. Frank breech	3 cases
D. Type of delivery:	
a. Perineal forceps and extraction	14 cases
b. Spontaneous parturition and breech extraction with Mauriceau-Smellie-Viet maneuver	3 cases each
c. Manual rotation O. T., to O. A.	2 cases
d. Perineotomy and repair	15 cases
e. Repair primary and second degree laceration	2 cases each
f. Repair sulcus laceration	1 case

SUMMARY

We feel that paraldehyde analgesia with perineal anesthesia has yielded satisfactory results in our hands.

It is our clinical observation that intra- and postpartum hemorrhage is decreased with this method. In one case a retroplacental hematoma necessitated administration of parenteral fluids. The uterus reacted well following completion of the third stage.

needle is then withdrawn until the point is just beneath the skin. It is then inserted so as to infiltrate beneath the cutaneous and mucosal surfaces at the site of the perineotomy, and 10 c.c. of the solution is injected. The procedure is then repeated on the opposite side, omitting the local infiltration for incision.



Fig. 1.—Point selected for insertion of needle. Needle brought to rest proximally and posterior to ischial spine.

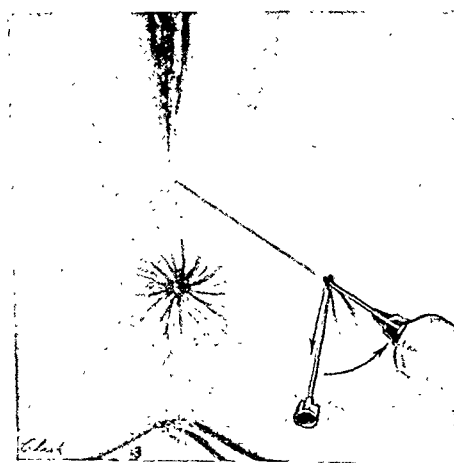


Fig. 2.—Infiltration at site of perineotomy.

By this method 50 to 60 c.c. of the anesthetic solution is adequate. As one becomes skilled in placing the solution, it will be found that smaller amounts are required. In a few cases, infiltration of the area selected for perineotomy was unnecessary, the bilateral nerve blocking giving complete anesthesia. However, we usually infiltrate this area and do not hesitate to use more of the solution if the anesthesia is not satis-

The placenta failed to separate and the patient began to bleed profusely from the uterus. An attempt was made to remove the placenta manually, but it seemed adherent to the superior and posterior lateral walls, and when it finally separated, inversion of the uterus followed, extending as far down as the introitus of the vagina. The uterus felt hard and contracted but was still bleeding. The vagina was packed, following which the patient's blood pressure dropped to 50/30 and her pulse rose to 140 per minute. Supportive treatment was of no avail and death occurred at 7:28 A.M. October 31, less than four hours after delivery.

At necropsy (A-38-1054) nothing unusual was noted about the head, neck, chest, and abdomen. The peritoneal surfaces were smooth and glistening, and there was no excess fluid. The uterus extended 7 cm. above the symphysis pubis. It was inverted and the fundus appeared sunken. The uterine ends of the Fallopian tubes and of the broad and round ligaments were drawn into the cavity formed by the inverted uterus.



Fig. 1.—Preparation from the fundus of the inverted uterus showing remains of chorionic villi and the compact layer of the decidua with no spongy layer intervening between these structures and the myometrium.

The uterus measured 12 by 12 by 8 cm. The fundus was inverted and its raw inner surface protruded into the vagina. The broad ligaments and the Fallopian tubes were drawn in so that at the top the ampullary portions of the Fallopian tubes and the ovaries were near to one another. They were of usual size and appearance.

MICROSCOPIC EXAMINATION

Myocardium.—There was a slight variation in the size of the myocardial fibers; in places they appeared vacuolated and their striations were indistinct. Many of the nuclei stained deeply and an occasional one was bizarre in shape. The tissue elements appeared somewhat spread apart. No changes were noted about the blood vessels.

Lungs.—The lumina of some of the bronchioles contained pink-stained material with a number of polymorphonuclear leucocytes and large mononuclear cells. The mucosa appeared wrinkled. Some of the air spaces were collapsed and others wide open. The interalveolar septa were narrow in some places and fairly broad in others.

Examination of preparations of the spleen, liver, pancreas, suprarenal glands, kidneys, and mammary glands revealed no pertinent changes.

The immediate puerperium has been encouraging. As shown in Table I, no case required catheterization. There was no morbidity. All tolerated regular diets following parturition.

The relative cost of paraldehyde analgesia and perineal anesthesia in our hands is approximately 9 to 11 cents per delivery, a financial factor of some importance in many institutions.

We agree with Greenhill⁵ that this method should not be used in the presence of local inflammation or in nervous, high-strung individuals.

The contraindications for general anesthesia in obstetrics are the indications for perineal anesthesia. This is well exemplified in our second table where forms of analgesia other than paraldehyde were used, but all cases were terminated with perineal anesthesia.

The authors wish to thank Drs. Bayard Carter, R. A. Ross, and H. F. Kane for permission to publish these cases.

REFERENCES

- (1) Ilmer, W.: Zentralbl. f. Gynäk. 34: 699, 1910. (2) Gellhorn, G.: J. A. M. A. 61: 1354, 1913. (3) King, R. W.: Surg. Gynec. Obst. 23: 615, 1916. (4) Torland, T.: Northwest Med. 29: 312, 1930. (5) Greenhill, J. P.: South. M. J. 26: 37, 1933. (6) Bradford, W. Z.: South. Med. & Surg. 98: 19, 1936. (7) Ruth, H. S., and Stiles, J. A.: Am. J. Surg. New Series 32: 217, 1936. (8) Walker, A.: AM. J. OBST. & GYNEC. 32: 60, 1936. (9) Ditter, F. J. A.: Northwest Med. 35: 150, 1936. (10) Urnes, M. P., and Timerman, H. J.: J. A. M. A. 109: 1616, 1937.

ACUTE INVERSION OF THE UTERUS POST PARTUM ASSOCIATED WITH PLACENTA ACCRETA

BÉLA HALPERT, M.D., AND PETER GRAFFAGNINO, M.D., NEW ORLEANS, LA.

(From the Departments of Pathology and Bacteriology and of Obstetrics and Gynecology of Charity Hospital of Louisiana at New Orleans and the Louisiana State University School of Medicine)

RECENT reports by Brett,¹ Peel,² Rucker,³ Williamson,⁴ Acosta-Sison and Mendiola,⁵ Cosgrove,⁶ Harer and Sharkey,⁷ and Phaneuf⁸ have discussed the principles involved in post-partum inversion of the uterus. Among the predisposing factors listed is placenta accreta, with or without manual separation.

In those tragic instances in which death occurs, permission for necropsy is not usually obtained and the anatomic cause of the inversion is therefore not ascertained. The case herein reported is the only instance in which such permission was obtained at the New Orleans Charity Hospital during the past twenty years. A reason for reporting this case lies in the fact that the chief cause, placenta accreta, is likewise unusual, and that fundal insertion of the placenta also played a part in the mechanism of inversion.

C. H., a 21-year-old, negro primipara, was first seen in the Outpatient Clinic of Charity Hospital of Louisiana at New Orleans Oct. 14, 1938. She was well developed, well proportioned, and well nourished. Delivery was expected in about two weeks. The patient complained of dyspnea on exertion, edema of the feet, and occasional nausea and vomiting. The blood pressure was 143/88. The fundus extended 29.5 cm. above the symphysis. Her pelvic measurements were within normal limits. The blood Wassermann reaction was negative.

The patient was admitted to the hospital Oct. 30, 1938. Labor began at 4 P.M. on the same day. The presentation was vertex. At 3:45 A.M. Oct. 31, 1938, a full-term child, weighing six pounds 15½ ounces, was delivered.

was great tenderness when the cervix was moved, and the cul-de-sac seemed to bulge. The uterus was enlarged and soft. Red blood count was 2,600,000, hemoglobin 67 per cent, white blood count 18,000, urine normal.

This appeared to be a typical picture of intra-abdominal hemorrhage caused most likely by a ruptured ectopic pregnancy. The uterus, however, was soft and larger than that usually found in simple ectopic pregnancies, and the diagnosis of intra-uterine pregnancy on July 3 made the present diagnosis of ectopic gestation uncertain.

Under cyclopropane anesthesia an exploratory laparotomy was done. Five hundred cubic centimeters of citrated blood from her husband was given during the operation. More than two quarts of blood were present in the abdominal cavity. The right ovary was as large as a golf ball, black and distended at the upper pole. The tubes were grossly normal and the uterus was normally pregnant, from two and one-half to three months in size. The left ovary was normal. Six hundred cubic centimeters of blood was aspirated in citrate solution to be used for an additional transfusion if necessary. A rapid salpingo-oophorectomy was done, along with resection of part of the left tube for purposes of sterilization. As much as possible of the free blood and the large clots were removed before closing. The appendix was left alone.

Her condition immediately after the operation was better than at the start and in twenty-four hours she was in good condition. The intrauterine pregnancy was not disturbed, and she was delivered spontaneously of a normal, healthy, seven-pound seven-ounce, female infant after an easy labor on Feb. 29, 1940, six months after the operation for the ovarian pregnancy.

The pathologist's report on the removed ruptured ovarian pregnancy was as follows:

"*Gross.*—The specimen consists of an ovary which measures roughly 3 cm. in diameter. One-half of this is solid, and the other is cystic. The cyst is partly filled with blood clot and lined by a thin membrane which grossly resembles a gestation sac. In addition, a tube is present measuring 5 cm. in length and less than 1 cm. in diameter. Grossly it is approximately normal in appearance.

"*Microscopic.*—Sections taken through the ovary show a number of atypical, somewhat degenerated but unmistakable chorionic villi, most of them covered by two layers of cells. One or two small masses of decidual cells also appear. A section taken through the tube shows the mucosal folds normal in appearance and very little evidence of an active inflammatory process.

"*Diagnosis.*—Ovarian pregnancy."

SUMMARY

A case of ovarian pregnancy is herewith presented. It fulfills Spiegelberg's criteria and is of particular interest, because a coexisting intrauterine pregnancy was present. This latter went to term undisturbed. So far as we have been able to determine, there is no report of an identical case in the medical literature.

REFERENCE

- (1) Pudney, W. K.: AM. J. OBST. & GYNEC. 33: 161, 1937.

Vrba, K.: An Explanation for the Headaches Which Occur After Spinal Anesthesia, Monatschr. f. Geburtsh. u. Gynäk. 109: 285, 1939.

Headache follows spinal anesthesia in from 3.2 to 7.8 per cent of cases. They occur more often when operations are performed in the first half of the menstrual cycle, than in the second half or in the menopause. The author believes this is linked up with some action of the glands of internal secretion, especially of the hypophysis. The greater the concentration of pituitary hormone in the blood, the more frequent are the headaches. Likewise, headaches occurred more often during the spring and autumn, seasons in which there are pronounced atmospheric changes.

J. P. GREENHILL.

Uterus.—Preparations from the fundus of the inverted uterus disclosed remains of chorionic villi and the compact layer of the decidua with little or no spongy layer intervening between them and the myometrium (Fig. 1).

SUMMARY

A case is reported of acute post-partal inversion of the uterus in a 21-year-old negro primipara. The uterus was completely inverted and extended to the introitus, drawing in with the fundus the proximal ends of the Fallopian tubes, the mesosalpinx, and the broad and round ligaments. The attachment of the placenta was chiefly over the fundic portion, and microscopic examination disclosed placenta accreta, the placenta being adherent to the uterine wall, without an intervening spongy layer. The uterine inversion was thus caused by placenta accreta, the fundic attachment of the placenta, and perhaps the attempt at its manual separation.

REFERENCES

- (1) Brett, P. G.: *Med. J. Australia* 1: 254, 1938. (2) Peel, J. H.: *J. Obst. & Gynaec. Brit. Emp.* 45: 821, 1938. (3) Rucker, M. P.: *South. M. J.* 32: 197, 1939. (4) Williamson, C. F.: *Bull. School Med. Univ. Maryland* 24: 32, 1939. (5) Acosta-Sison, H., and Mendiola, N. D.: *J. Philippine Islands M. A.* 19: 395, 1939. (6) Cosgrove, S. A.: *AM. J. OBST. & GYNEC.* 38: 912, 1939. (7) Harer, W. B., and Sharkey, J. A.: *J. A. M. A.* 114: 2289, 1940. (8) Phaneuf, L. E.: *Surg. Gynec. Obst.* 71: 106, 1940.

SIMULTANEOUS OVARIAN AND INTRAUTERINE PREGNANCY

G. C. MILNOR, M.D., F.A.C.S., AND H. E. BOWLES, M.D.,
HONOLULU, T. H.

PUDNEY¹ has reported the simultaneous occurrence of a left ovarian pregnancy and a right tubal pregnancy, but a review of the literature available to us here fails to show any record of the coexistence of a primary ovarian pregnancy with a normal intrauterine gestation. We wish to offer the following case as one of this type. It fulfills Spiegelberg's criteria inasmuch as (1) the tube of the affected side was intact and had no organic connection with the gestation sac; (2) the fetal sac occupied the position of the right ovary; (3) the right ovary, containing the sac, was attached to the uterus by the ovarian ligament, and (4) definite ovarian tissue could be seen in the sac wall. Furthermore, the tube of the affected side showed no microscopic abnormality except for a slight edema.

Mrs. P., aged 28 years, was delivered of her fourth child on Jan. 19, 1939. All 4 pregnancies and deliveries were quite normal. Her past history was essentially negative except for a progressive otosclerosis as manifested by increasing deafness. Her menses began at thirteen and were normal every twenty-eight days except when she was pregnant. She had had no miscarriages.

On July 3, seven months after the birth of her last child, she was examined and found to be about two months' pregnant. Menstrual periods had begun two months after delivery. When seen, she had missed two periods and had the symptoms of pregnancy. She wanted an abortion, but this was refused and she was advised to have the child and be sterilized after the delivery. She was not seen again until August 23 at which time she gave the following history:

From July 3 until August 23 she felt quite well except for some nausea. At 1 A.M. on August 23 she was suddenly awakened with very severe abdominal pain. This grew worse and she fainted twice in an hour. She became pale and perspired profusely. There was also pain in her left shoulder, she vomited several times, and became dyspneic. When seen she was pale and in shock. The skin was cold and clammy, pulse 130, respiration 30, temperature 97° F., abdomen distended and very tender. A marked blueness was present around the umbilicus (Cullen's sign). Vaginally there

sapremia. The patient was discharged on the fourteenth postoperative day in good condition. The blood count at this time showed hemoglobin 78 per cent and red blood count 4,000,000.

We have presented a case of traumatic hematoma of omental adhesions in late pregnancy and wish to emphasize the case in which this condition may resemble a premature separation of the placenta.

BILATERAL FIBROMA OF THE OVARIES COMBINED WITH A DEGENERATING ADENOMA OF THE RIGHT BREAST

EVA HAUMEDER, M.S., M.D., NEW HAMPTON, IOWA

(From the New Hampton Clinic)

FIBROMAS of the ovary, though not as uncommon as one might be led to believe by the scattered reports in the literature, are nevertheless an interesting finding, especially if the lesion is bilateral and combined with a degenerating cystadenoma of the breast.¹⁻⁵

A white patient, 63 years of age, married, presented herself with complaints of pain and discomfort in the lower abdomen of about three to four weeks' duration.

Her menstrual history showed nothing unusual, having had her menarche at 13 years and menopause at the age of 50. She has three living children.

The physical examination revealed a well-nourished patient. The abdomen was enlarged, without rigidity or tenderness, by a movable, firm tumor in the lower quadrant, not connected with the uterus. There was no indication of the presence of ascites, no palpable glands, no edema. In the right breast a rather soft, nodular tumor, which was freely movable, could be palpated.

The patient was submitted to an exploratory operation at which time pan-hysterectomy was performed. The tumor in the right breast was removed at the same time. There was no fluid found anywhere in the body, neither abdominal nor pleural.

Pathologic Report.—The specimen consisted of uterus, both tubes and ovaries, also of the nodule from the right breast. The left ovary weighed 3,560 Gm. and measured 25 by 19 by 10.7 cm., and the right measured 10.5 by 8.4 by 6 cm. and weighed 1,520 Gm. The tumors were firm, showed a nodular surface, and were of grayish white color. On cut section the color was pearly white, glistening and of a coarse, fibrous, whirl-shaped structure. There were several yellowish areas of a softer consistency, as well as a cystic degeneration in the upper pole of the right ovary, measuring 5 by 4 by 3.9 cm. Signs of hemorrhage were also present. The left ovary was of the same structure and contained several much smaller cysts. The microscopic picture presented the usual structure of fibromas, interlacing bundles of fibrous tissue as well as a few muscle fibers. The large fibrous cells appeared mature with normal nuclei and comparatively small nucleoli and were arranged regularly. There were no mitotic figures seen. Some myxomatous and hyaline degeneration was present, as well as several areas of necrosis. The cysts showed a lining of a layer of flat epithelial cells.

The tumor of the right breast was a soft, hemorrhagic, nodular mass 4.5 by 3.5 by 3 cm. in size; on section it was cystic, reddish brown, gelatinous, and encapsulated. The microscopic pictures presented within a mucinous degenerated stroma a few glands, many dilated to cysts, the lining being a single layer of epithelial cells. There was marked round cell infiltration of the tissue as well as areas of hemorrhage.

The patient's recovery was uneventful, and after a period of five years, she is alive and well.

The tumor reported here did not cause any accumulation of fluid in the body, as is occasionally reported in the literature. It must have grown rather slowly because of the lack of symptoms and the patient's relative well-being. It would be interesting to speculate whether the tumor of the breast had any connection with the ovarian tumors, as ovarian tumors connected with changes in the mammary glands do occur.

TRAUMATIC HEMATOMA OF OMENTAL ADHESIONS SIMULATING PREMATURE SEPARATION OF PLACENTA

LOUIS J. ZUPP, M.D., AND VICTOR MAYER, M.D., WARREN, PA.

(From the Maternity Division, Warren General Hospital)

WE PRESENT a case which raised an interesting diagnostic problem. We realize the rarity of such a combination of factors but feel that there is likelihood of more frequent occurrence, in view of the increasing number of pregnant women coming to the delivery room with an abdominal scar as evidence of an earlier appendectomy or of pelvic surgery. The possible occurrence of hematoma of omental adhesions might well be considered in cases of trauma to the abdomen in late pregnancy where previous abdominal surgery has been done.

Mrs. J. B., aged 21 years, was brought to the Maternity Division of the Warren General Hospital on March 9, 1940, at 2:00 A.M., complaining of severe generalized abdominal pain. She had received no prenatal care during this, her second pregnancy. Her last menses was dated vaguely during the middle of July, 1939, making this approximately her eighth month of pregnancy. Abdominal pain had begun about twelve hours prior to admission and was of increasing severity. There was nausea but no vomiting. (Several days later, the patient revealed that a short time prior to the onset of abdominal pain, she had become much alarmed when her baby developed convulsions, and she had rushed out into the open on an icy walk. She slipped and fell, striking her abdomen.)

Fifteen months prior to the present admission, the patient was admitted to the maternity division in labor with a full-term pregnancy. Examination at that time showed a generally contracted pelvis with direct evidence of cephalopelvic disproportion. Classical cesarean section was done and a live baby obtained. Convalescence followed a septic course with the patient developing a pyometra. Following a cautious dilatation of the cervix, with the institution of drainage, the patient recovered. She was discharged on the twenty-third hospital day in good condition.

Examination on admission disclosed a poorly developed and undernourished white female; heart and lungs normal; blood pressure 110/88. The size of the uterus was that of an eight months' pregnancy. The entire abdomen was exquisitely tender. The uterus felt very firm and as if persistently contracted. Fetal heart sounds were barely audible in the left lower quadrant. Fetal position was diagnosed as L.O.A. Pelvic measurements showed a generally contracted pelvis. Vaginal examination revealed a tender cervix with neither dilatation, effacement, nor bleeding. A diagnosis of premature separation of the placenta with concealed hemorrhage was made and immediate abdominal section planned.

A classical cesarean section was done. On opening the peritoneal cavity, the omentum was found adherent to the fundus and the anterior uterine wall. A large hematoma was present in the omentum overlying the uterus. No fresh bleeding points were evident. The omentum was separated from the uterus with ease. On opening the uterus, the cord presented and was not pulsating. The baby was delivered with some difficulty. No apparent abnormality was found in the placenta. The baby responded poorly to stimulation and died shortly afterward, although placed in a Drinker respirator.

The mother was returned to the ward in good condition. Her blood count at this time showed hemoglobin, 50 per cent; red blood count, 2,500,000; color index, 1; white blood count, 7,600; differential count: 86 per cent segmented polymorphonuclear leucocytes, 6 per cent nonsegmented polymorphonuclear leucocytes, and 8 per cent lymphocytes. She was given venoclyses of glucose in saline, and a transfusion of 600 c.c. of citrated blood. Convalescence was normal except for a transient

delivering the males, another fetus, a female, was discovered within a separate bag of water and with a separate placenta. The males weighed 4 pounds, 5 ounces, and 3 pounds, 10 ounces, and the female 3 pounds.

The males were apparently eight months' babies but the female, in addition to being much smaller, had the development of a seven months' fetus. The males breathed spontaneously. There was considerable difficulty in resuscitating the female, but after she began to breathe no further trouble was encountered. One of us (D. C.) assumed immediate charge of the triplets and at the end of six months they weighed 15 pounds, 8 ounces, 16 pounds, and 13 pounds, 6 ounces, respectively. They have never been ill since birth and are in excellent physical condition. On account of the economic condition of the family, the babies were kept in the hospital.

WEIGHTED ABDOMINAL RETRACTOR*

J. W. VISHER, M.D., EVANSVILLE, IND.

AN IMPORTANT problem in gynecologic surgery is retraction of the sigmoid and small intestines while operating upon the pelvic viscera. The Trendelenburg position is of considerable help, but in addition an abdominal roll of gauze is usually required to pack off the intestines. However, gauze is a foreign body which irritates the peritoneum and predisposes to postoperative abdominal distention and adhesions. Also, retraction is often inadequate as the intestines usually crowd down again into the operative field.

The retractor illustrated is the result of much study and experimentation. The curvature of the blade is similar to that of the female pelvis and fits into the cul-de-sac. The handle is forked, to prevent rotation, and the entire instrument is of sufficient weight (about three pounds) to hold back the intestine and leave an

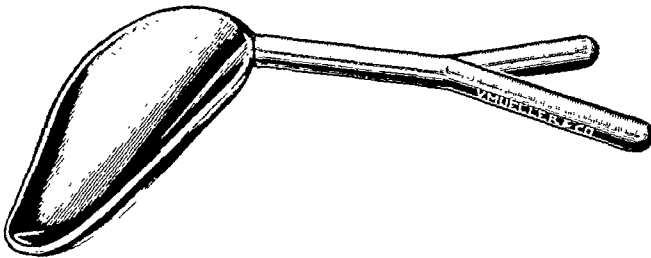


Fig. 1.

inch or more free working space between the uterus and the blade. The patient is placed in the Trendelenburg position, the abdomen is opened and a Balfour self-retaining retractor is inserted. The intestines are then pushed into the abdominal cavity, and the blade of the weighted abdominal retractor is placed in the cul-de-sac, while the handle rests upon the abdominal wall.

Its use facilitates all operations on the pelvic viscera, but it is especially valuable in hysterectomies. It can also be used in gall bladder operations. In addition to its value as a retractor, it has several other advantages. It protects the abdominal viscera from infection and collects the blood where it can be easily seen and removed. It decreases the manipulation of the intestines to a minimum, which materially decreases postoperative distention and adhesions.

REFERENCES

- (1) *Clark, E. D., and Gabe, W. E.*: AM. J. OBST. & GYNEC. 6: 603, 1921. (2) *Fullerton, W. D.*: Surg. Gynec. Obst. 18: 451, 1914. (3) *Hellman, A. M.*: Ibid. 20: 692, 1915. (4) *Hoon, Merle R.*: Ibid. 36: 247, 1923. (5) *Meigs, Joe Vincent, and Cass, John W.*: AM. J. OBST. & GYNEC. 33: 249, 1937.

VIALE TRIPLETS DELIVERED BY CESAREAN SECTION

LINTON SMITH, M.D., AND DON CATHCART, M.D., ATLANTA, GA.

(From the Crawford W. Long Memorial Hospital)

THE only report that we found in the literature of triplets being delivered by cesarean section with survival of all three babies, was by C. H. Roberts, in the *British Medical Journal*, July 2, 1927. We are, therefore, reporting our experience because of the rarity of such cases and, because of the uniqueness of identical boys with a triplet sister one month younger than they.

CASE 91315.—The mother was a well-developed white woman, aged 29 years, who had been married eight years and had never been pregnant. Her health had been good except for infected tonsils for which a tonsillectomy had been done four years previously. She consulted one of us (L. S.) Feb. 10, 1939, after missing her second menstrual period, complaining of much nausea and vomiting. An examination showed her to be two months pregnant, which corresponded with her menstrual history. Her blood pressure was 119 systolic and 87 diastolic. Urinalysis was normal and Wassermann negative.

The nausea and vomiting persisted in spite of all treatment until the end of the seventh month which suggested an unusual degree of toxemia. At that time a careful examination showed a twin pregnancy with one fetus occupying a left occipito-anterior position, with the head rather low in the pelvis, and the other fetus in a breech presentation. An x-ray examination was not made for economic reasons and the presence of the third fetus was not recognized.

Dec. 6, 1938 being the first day of the last menstrual period, Sept. 12, 1939 was given as the expected date for delivery. The patient was seen weekly and her blood pressure and urinalysis at each examination revealed nothing abnormal, but on July 25 her blood pressure had increased from 119 to 140 systolic and 87 to 98 diastolic, and there was a small amount of albumin in her urine. She was placed on a milk diet and kept in bed. One week later her blood pressure had increased to 149 systolic and 104 diastolic, there was a large amount of albumin in her urine, and she was edematous. She was kept in bed, given a milk diet and saline purges, and an immediate termination of her pregnancy was suggested but declined.

On August 12 at 6 A.M. slight pains began, and she was taken to the hospital where she was given two ounces of castor oil and a hot enema followed by two minims of pituitrin subcutaneously every twenty minutes for four doses, but her pains continued irregular and weak. There was no dilatation of the cervix, and the lower uterine segment had not become obliterated. Her blood pressure was now 170 systolic and she was very edematous. No vaginal examination had been made, and a cesarean section was urged as she was considered definitely a pre-eclamptic. Two consultants agreed in the diagnosis and advised that an immediate operation be done. Both fetal heart sounds were of good quality, 150 and 156, respectively; the third fetal heart sound was not heard.

At 11 A.M. she was sent to the operating room and 150 mg. of novocaine were given intradurally, and immediate delivery by cesarean section was accomplished. On opening the uterus through a high left rectus incision, a male baby in the right occipitoanterior position was found and delivered; the other male baby which was in a breech position was then delivered. Both babies were in a common amniotic sac and their cords were attached to a common placenta. After

with rapid decline in albuminuria and blood pressure is, in a sense, a confirmation of the original diagnosis of the eclamptic type of toxemia, for the nephritides usually do not act in any such manner. When, on the contrary, after a typical episode of eclampsia or pre-eclampsia, there does not occur, following death of the fetus or termination of the pregnancy, a sharp diuresis, or when such signs as hypertension and albuminuria persist for six or more weeks post partum, one is usually dealing with a superimposed nephritis, or the condition has been a nephritis from the very beginning.

Progressive eye-ground and urinary findings should thereafter be watched for. Typically, the urine in the eclamptic group contains considerable albumin, mostly as serum-albumin, which usually boils solid just before the anuric stage is reached. There is in the pre-eclamptic patient usually a conspicuous absence of red blood cells in the urinary sediment, although hyalin and granular casts in showers are rather usual. The Addis urinary sediment count frequently presents a picture of nephrosis, namely, a marked increase in hyalin casts and albumin with a normal number of red blood cells. A 12-hour urinary red blood cell count above 500,000 suggests the presence of a concurrent hemorrhagic nephritis.

The blood chemistry in pre-eclampsia typically reveals a low nitrogen rest—a low or normal urea nitrogen, a high uric acid (often 5 mg. per cent or more), a tendency to low blood sugar, usually a high blood cholesterol until late in pregnancy,¹⁻⁵ when it may become low. Symptoms are sparse. They are, for the most part, dull headaches, spots before the eyes, and tightness of the rings on the fingers. The occurrence of marked headache and epigastric pain is often the herald of an approaching crisis. Young primiparas are most commonly afflicted, although older primiparas and, less often, multiparas suffer. The victims often show an endocrine anlage, such as hypothyroidism or that roundness of the hypopituitary individual.

Frequently, there is a history of previous food preference along the lines of carbohydrates rather than proteins,⁶ such as meat, fish, eggs, and milk. The typical European breakfast of coffee and rolls and the "flapper" type of luncheon, soup, fruit salad, and tea, are found to be among the food habits of many of these patients. It may be of interest at this point to state that Ashe and Mosenthal⁷ made a study, some time ago, of the average protein ingestion of nonpregnant adults in the New York area and, to their surprise, found that it was well below 50 Gm. daily, far below the accepted needs for the ordinary adult, not alone the gravid female who is building fetus and appendages and would obviously be obliged to tax her own body for the building stones.

Evidence is insufficient even to suggest that faulty diet is the cause of eclamptic toxemia; to date, there is no real evidence that the diet plays more than a contributory role. There can, however, be no doubt that a pregnant female, using a diet of 50 Gm. or less of protein, will be far more susceptible to water retention^{6, 8-10} and edema than her more adequately nourished sister. One does not have to look to the pregnant state to establish this principle on a firm foundation; it is seen in cardiac patients with increased peripheral venous pressure. Even a slight diminution in the normal concentration of their plasma albumin or protein will, in the presence of a heightened venous pressure, swing these cardiac patients to the side of tissue edema. Certainly the pregnant woman, especially the primipara with firm rigid

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

THE TREATMENT OF PRE-ECLAMPSIA*

A RATIONALE FOR DIETARY REGULATION IN THE PRECLINICAL STAGE

GEORGE E. ANDERSON, M.D., F.A.C.P., BROOKLYN, N. Y.

MORE and more toxemia of pregnancy is becoming an "internist's disease," for its romantic ramifications into theoretical realms extend far beyond the scope of obstetrics and into the fields of metabolism, endocrinology, physiologic chemistry, and the pathologic physiology of such systems as the renal, the hepatic, and the vascular. No longer is the clinical work-up of any toxic gravida complete without a careful medical survey. It has been well said that toxemia of pregnancy is the "disease of theories," for its etiology and mechanism are still quite nebulous. It is likely that, in due time, it will be demonstrated that toxemia of pregnancy is a large group of diseases, with individual clinical pictures, each of which depends upon its respective percentage make-up of four main factors, the renal system, the endocrine system, the hepatic system, and the vascular system. One syndrome will be predominantly "liver," another vascular, another renal, another endocrine—but none in pure form.

The present consideration does not, except by way of differential diagnosis, include the chronic nephritides, states which are not toxemias of pregnancy at all since they antedated the gravid state and will continue to exist post partum—to be sure, with increased severity as a result of the unfortunate coincidence of pregnancy. There is little excuse in the carefully studied case for failure to recognize members of this nephritic group. The issue has unfortunately been beclouded by such an indefinable term as: "low-reserve kidney," which has often been used to cloak a bad differential diagnosis. The present consideration will touch on late pregnancy toxemia, the eclamptic group, or the toxemias of the last trimester of pregnancy. These are characterized: (1) by an inordinate gain of body weight throughout pregnancy—in the early months as latent water-retention, in the last trimester as frank edema; (2) by low or normal blood pressure in the early months followed by rather sudden climbing blood pressure in the last trimester; (3) by normal urinary findings in the early months, followed by frank albuminuria in the latter months of gestation. This group of signs may eventuate in anuria and convulsions at the time of reaching their peak, or they may, on the other hand, be sharply interrupted by a termination of the pregnancy, spontaneous or induced, whereupon there is characteristically a voluminous diuresis, gradual reduction in blood pressure, and a clearing of the albuminuria. This sharp diuresis

*Read, by invitation, at a meeting of the Brooklyn Gynecological Society, as part of a program on Maternal Mortality, May 3, 1940.

without saying that ketones, despite their dehydrating effect, should be destroyed in or removed from the body by adequate forced glucose utilization. Ordinarily, however, the careless unlimited administration of water is to be deprecated in the pre-eclamptic patient.

Among good empiric dietary measures employed in the past in pre-eclamptic toxemia is the copious use of milk. It may be stated without reservation that this has, inadvertently, saved many a life. Its high potassium and calcium content has favored diuresis. The protein content of one and one-half quarts of milk as usually prescribed approximates 50 Gm., making up, somewhat, for the protein starvation often otherwise purposely imposed by the medical attendant.

Just why should one's anxiety be so keen that the patient receive adequate protein in her diet? The old dictum that, since the patient is pouring out albumin in the urine, albumin-producing foods should be withheld, is as fallacious as was the principle of withholding sugar-producing foods from the diabetic patient because he is losing sugar in the urine. We now find that the diabetic individual does much better when he is receiving a liberal carbohydrate intake, whether or not he requires insulin. Several facts point to the extreme importance of making certain that the pre-eclamptic gravida is in nitrogenous equilibrium. First, she is building fetus, uterine muscle, and placental tissue; the building stones are better supplied than extracted from her own organism. Second, early in pregnancy the pre-eclamptic patient usually runs a low basal metabolic rate; protein, by its specific dynamic effect, tends to stimulate metabolism and thereby to burn off excesses of cholesterol. Late in pregnancy, these same patients frequently develop an accelerated metabolic rate far in excess of what would be represented by the additional gestational tissue; under such conditions of increased burning, there are greater protein demands on the maternal organism—they should certainly be supplied. Third, a progressive albuminuria is often found to cause some albumin depletion; it should be replenished to maintain within the vessels effective osmotic pressure and thereby forestall tissue edema.^{6, 8} For these purposes animal proteins are far more efficient than vegetable proteins—at least 100 per cent more effective.

Let us next consider the case *against* protein feeding. That pathologic pictures identical with nephritis¹³ have been produced in experimental animals by the feeding of animal protein cannot be denied. An excellent refutation to this argument, however, is the fact that white rats are herbivorous and certainly man does not fit into the same category. Besides, the amount of protein fed was enormous compared with man's intake. Today there is no worthwhile medical^{14, 15} authority who denies his most severe nephritic patient at least a maintenance of animal protein. Whereas the nephritic patient on a protein-free diet formerly died prematurely by virtue of his physician's exacting diet prescription, today she lives just so long as her kidneys can carry on their function rather than so long as there still remain some of her own tissue proteins which she can use up in lieu of a deficient diet.

Let us feed our patient not an excess of protein but an amount adequate for her needs. Let us, however, also prevent unnecessary protein catabolism and breakdown by sparing the body proteins. One will thereby take the load from the renal excretory mechanism for urea excretion. This sparing can unquestionably be accomplished by supplying the patient with that great protein sparer, carbohydrate. The

abdominal wall, has the wherewithal for increased venous pressure. Add to this same rigid abdominal wall multiple gestation or hydramnios, complications long recognized as favoring eclamptic toxemia, and even the slightest discrepancy in plasma protein becomes greatly magnified in its significance in favoring tissue water retention. The careful and interesting work of Strauss,^{6, 8} of Boston, has produced incontrovertible evidence of this.

While we do not know the cause of eclampsia, we are very cognizant of certain circumstantial disorders which accompany the syndrome, much as we are in the "set-up" of malignancy. We can, however, in eclampsia, employ far more rational therapy than in malignancy, and obviously we can more often steer a relatively safer course, despite our ignorance of etiology. Nebulous as may be our conception of its etiology, we should nevertheless employ *rational* therapy whenever possible, rather than empiric, unless it is found that the latter is definitely not harmful. Thus, the empiricism of colonic irrigation with bicarbonate of soda, of sweating the patient to make up for a supposedly deficient renal function, of imposing on her the burden of caloric or protein starvation, is of the past and is much in the same category as massaging an acutely inflamed appendix.

The toxic patient may *not*, in the light of even the meager knowledge available, be viewed as a *pure* nephritic problem or an endocrine or a metabolic problem, but must be viewed in a more collective sense.

The cause of water-logging in the eclamptic syndrome is not known; nevertheless, methods of treatment which encourage water retention should logically be avoided. First of all, sodium, whether this be in the form of sodium chloride, sodium bicarbonate, or sodium bromide, should be scrupulously reduced to a minimum, since its accumulation in the extracellular tissue spaces makes for water affinity. One occasionally sees patients placed on a salt-low diet of 2 to 3 Gm. daily and at the same time given sodium bromide by rectum at the rate of 4 to 6 Gm. a night for sedation. These same patients sometimes receive daily colonic irrigations of sodium bicarbonate in 5 per cent solution. Such divergent therapy could never pass any therapeutic rationalist. We used to fear the chloride ion and blame it for edema; now we commonly use chloride of ammonium and calcium chloride for their acidifying effects in order to produce diuresis and a mobilization of sodium from the tissue spaces.

The so-called "hydration method" of Newburgh,^{11, 12} recently published by Alvarez, in which method unlimited amounts of water are given by mouth, is, in truth, a dehydration regime—since, under certain conditions, water is one of the best diuretics. The "hydration method" is effective in the pre-eclamptic patient *when ammonium chloride is concomitantly given*, for it mobilizes and washes out sodium in the presence of an acid diuresis. I can see no point, however, in insisting on a neutral ash diet and then thoroughly acidifying the individual with ammonium chloride. One can readily recognize the principle aimed at, namely, the avoidance of an alkaline ash diet which otherwise would favor water retention. The old vogue of alkalinizing the eclamptic patient by drug or diet is born of ignorance. Even the ketones occasionally found in the blood and urine of these patients late in their disease could be serving the purpose of dehydration rather constructively, if it were not for their known irritating effect on the renal tubules, thereby heightening any existing nephrosis. It goes

Bartholomew¹ has suggested burning-off the excess of cholesterol in the blood by thyroid feeding *early* in pregnancy, since there is usually at this time a low basal metabolism. It is doubtful whether thyroid in these patients would have any more effect than it does in typical lipid nephrotics, patients who are notoriously resistant to this hormone. Moreover, thyroid feeding in pre-eclamptic females is not a new concept by any means, nor has it in the past been too successful in improving the clinical picture of the toxic patient. The thyroid discrepancy is not necessarily intrinsic in the thyroid gland; one must bear in mind that the very lowest²⁴ metabolic rates known to science come in association with destructive diseases of the anterior lobe of the pituitary gland. Unfortunately, the scope of this paper will not permit a consideration of the endocrine implications of the subject. I cannot, however, leave the endocrine field without stressing at least one practical point learned by sad experience—that there *may* be something in the original work of Hofbauer²⁵⁻²⁹ in 1918 in respect to the posterior pituitary as being an etiologic factor in eclampsia. "Pituitrin" is so definitely antidiuretic that it is without doubt the most effective agent available for therapy of the polyuria occurring in diabetes insipidus. Dieckman, Michel,³⁰ and others have shown that patients suffering from the toxemias of pregnancy are extremely sensitive to the vascular-constricting and antidiuretic effects of "pituitrin." Best,³¹ of insulin fame, has pointed out that the same type of fatty liver which occurs in pregnancy can be artificially produced in animals by repeated injection of "pituitrin." One should derive a certain moral, even without further evidence, that "pituitrin" or its analogues should never be used in any toxic female or in anyone who in previous pregnancy had pre-eclampsia or eclampsia. I am thoroughly convinced that I have seen deaths occur in pre-eclampsia as a result of acute renal shutdown incidental to even a single dose of "pituitrin" in a highly sensitive individual.

The importance of the endocrine system, the pituitary, the estrogen group,³² estriol, etc., may ultimately furnish the solution of the problem of etiology in eclampsia. Certainly, it cannot be discarded as being an unrelated factor any more than can the liver.

What is the status of the vascular and renal systems in this disease? It has been suggested that they suffer *from*³⁴ the disease, rather than that they *cause* the disease. It is likely that the effect of the toxemia on these tissues actually determines whether the victim goes into convulsions or "rides out the storm" for the time being. Vascular spasm is the *effect*, not the cause. To be sure, if the spasm lasts long enough, it will be translated into permanent vascular damage and gross pathology. Intracranially this spasm seems in some way to be linked up with edema in producing the convulsive state of eclampsia.

Herrick and Tillman³³ feel that renal disease is the *result* rather than the *cause* of the eclamptic syndrome, that the differentiation between mild nonnephritic and severe nonnephritic toxemia is merely a matter of degree rather than kind. From their statistics, one may anticipate that more than half of those who suffered from eclampsia and are still alive three years after their toxic episodes will show evidence of permanent hypertensive vascular disease. It is the *ultimate* renal and vascular damage that one should consider in evaluating the status of the toxic female—what will she show or where will she be

normal human being will always, if it is available, metabolize carbohydrate in preference to, and more efficiently than, protein and fat. This truth is beautifully demonstrated in diabetic patients who will carry on and very successfully maintain body-weight on several hundred calories less per day than ordinarily anticipated, provided most of the food ingested is in the form of carbohydrate.¹⁶ On the other hand, if insufficient carbohydrate be given, the human being runs in negative nitrogenous balance since he is forced to break down his own tissue-protein as well as the ingested protein for energy purposes.

Whereas carbohydrate spares protein, this function is not the main advantage of a high carbohydrate intake for the pre-eclamptic or the eclamptic patient. The liver is generally regarded as at least one of the "shock tissues" in eclampsia. It bears the brunt of wear and tear even through normal pregnancy as is evidenced by the fact that practically every liver in pregnancy is a fatty liver, much as is the liver in animals receiving large injections of "pituiratin."¹⁷ Whenever fat fills the liver, the ability of that organ to store glycogen is usually greatly impaired. The early hypercholesteremia of those patients who are destined to suffer from pre-eclampsia predisposes to fat deposits in the liver, much as it does in diabetic patients, who, incidentally, are also very prone to develop the eclamptic syndrome. There is good evidence that one can,^{18, 19} to a certain degree, delay or even prevent this lipid accumulation in the liver by forced carbohydrate feeding and utilization (which really means forced glycogen storage in the liver). Hypercholesteremia does play a role in toxemia of pregnancy, possibly, as Colvin and Bartholomew¹⁻³ have suggested, by way of predisposing the patient to placental infarcts. Much has lately been written about these infarcts²⁰ and the roles of arginine and guanidine, arising therefrom, in producing the smooth-muscle phenomena of pre-eclampsia and the convulsive state. The theory is very interesting, but why do not otherwise normal pregnant women who not infrequently develop²¹ placental infarcts go into eclampsia? The answer does not seem to be too difficult—it is probably because normal pregnant women still have livers which can deaminize and destroy these toxic amines more efficiently than can the damaged liver of the pre-eclamptic patient. There are good reasons for incriminating the liver in the eclamptic syndrome: (1) blood uric acid is high in these patients at a time when there is no inability of the kidneys to excrete this substance; (2) blood urea is characteristically low (the liver is the only organ in the body which can elaborate urea, and presumably in the eclamptic patient it is not succeeding well in doing so)—some of the lowest ureas on record are met in fatal cases²² of eclampsia; (3) true eclampsia is far too frequently associated with the post-mortem findings of liver damage for such pathology to be mere coincidence.

Apart from pregnancy, it has been taught that carbohydrate^{18, 19} is one effective agent available to protect the liver; when glycogen is heavily stored therein, this organ becomes less vulnerable. Witness the development of liver cirrhosis in long-standing, uncontrolled hyperthyroids²³ and other states in which an abundance of suprarenalin constantly makes the liver drop out into the blood stream, as glucose, its stores of glycogen. While glycogen can coexist in the liver with fat, it is most usual to find one present at the expense of the other. One of the few means we have at our disposal for safeguarding the liver is adequate carbohydrate ingestion (or parenteral glucose).

TABLE I. COMPARISON BETWEEN THE VALUES OF THE AVERAGE NORMAL DIET AND THE DIET RECOMMENDED IN PRE-ECLAMPSIA*

CARBOHYDRATES	PROTEINS	FAT	CALORIES
<i>Average Normal Diet</i>			
350	70-100	90-100	2,500 to 2,700
<i>Diet in Pre-eclampsia</i>			
300-350	150	55-60	2,295 to 2,540
<i>Animal Protein About 110 Gm. Daily—Represented by</i>			
PROTEIN VALUE			
Whole milk	1 pint	15.8	} 112 Gm. (animal)
Skim or buttermilk	1 pint	16.3	
Egg	One	5.9	
Meat (very lean) or Fish	½ lb.	74.4	
Vegetable protein		38.0	
Total		150 Gm.	

In order that fat and cholesterol may be kept at low levels, avoid more than 1 egg daily, or more than 3 teaspoonfuls of butter, or 3 tablespoons of heavy cream, or the following high cholesterol-containing meats:

Pork, duck, goose, brains, sweetbreads, corned beef, canned tongue, butterfish, halibut, tuna, mackerel, smoked halibut, smoked herring, canned sardines, salmon, roe.

*In The Brooklyn Hospital, "Diet Control" by Anderson and Eschweiler is used to establish these values in menu form.

dynamic heat effect, and also for maintaining a normal level of blood plasma protein. Weight gain will usually remain normal on this diet.

On such a regimen many a predisposed individual will evade pre-eclampsia, which should if possible be treated long *before* it becomes clinically evident. By the same token, it is likely that after the development of albuminuria, hypertension, and gross edema, diet will accomplish very little from a corrective standpoint, since the necessary time factor for correction is too short. On the development of gross signs of pre-eclampsia, the patient should, of course, be hospitalized. The diet should be continued, with proportionately *more* milk than meat in order to favor diuresis and to replenish (if depleted) blood cholesterol, provided, of course, an increased metabolic rate, as is usual at this time, has supervened. If anemia is present, blood transfusion is in order. If plasma proteins are found to be even slightly reduced in amount, they should be replenished by serum or blood transfusion.

If after a two- or three-week period of diet, bed rest, and intelligent expectancy, there is not marked amelioration of all signs, or if there is a progression in *any* of the signs, induction of labor should be advised in the interest of the mother and her future life-expectancy. Procrastination beyond a three-week period is hazardous and may result in irreversible, irreparable renal or vascular damage.

It has been stated, as applied to uterine hemorrhage: "The only safe uterus is an empty uterus." When the toxic gravida does not rapidly respond to rational therapy, it would seem that the *same* principle should certainly be invoked.

REFERENCES

- (1) Colvin, E. D., and Bartholomew, R. A.: AM. J. OBST. & GYN. 37: 584, 1939.
- (2) Bartholomew, R. A.: J. A. M. A. 111: 2276, 1938.
- (3) Bartholomew, R. A., and Colvin, E. D.: AM. J. OBST. & GYN. 36: 909, 1938.
- (4) Dieckmann, W. J.: Arch. Int. Med. 53: 71, 188, 540, 1934.
- (5) *Idem*: AM. J. OBST. & GYN. 26:

in five or ten years hence, if one "pig-headedly" insists on her carrying to certain viability? What price a viable baby?

On the basis of these concepts, how can one rationally treat the pre-eclamptic female? The first step in treatment is of course a correct diagnosis. If, early in pregnancy, there is a hypertension with cardiac hypertrophy, the patient is obviously not suffering from pre-eclampsia, but in all probability from a so-called essential hypertension or a chronic nephritis. Continuation of the pregnancy, should, in the best interests of the patient, be discouraged. She is not entitled to even a trial of pregnancy if her future is to be considered unless with a full knowledge of the possibilities she would desire to gamble. Especially is the continuance of pregnancy to be deprecated if the patient shows an abnormal Addis count, or a faulty urea clearance, or a pyelitis, or a pyelonephritis (Zimmermann and Peters³⁴). If one would put credence in Goldblatt's³⁵ theory of renal ischemia as producing essential hypertension, then by virtue of the possibility of pressure phenomena incidental to pregnancy one should recommend interruption in all cases of early hypertension whether or not there be concomitant renal findings.

The pre-eclamptic patient presents a far different picture. There is more of a range of safety in her case, although one must accept the fact that even she stands a "fifty-fifty" chance of premature vascular disease or early demise from a hypertensive vascular disease within a few years after her toxic episode.

The treatment of pre-eclampsia should really be started *before* the disease actually has developed in the individual. One should watch for and scrutinize the vagotonic type of patient with low blood pressure with vasospastic cold extremities, with spastic retinal vessels,¹ with slow or irritable pulse, and a history of bowel crises, especially if that patient is of the round hypopituitary or of the hypothyroid type. If she, in addition, carries a high cholesterol, a low or low-normal basal metabolism, a low blood sugar, and with the onset of pregnancy if she shows a rapid gain in body weight, she should be considered a very likely candidate for pre-eclampsia. Dietary treatment should *immediately* be instituted rather than waiting for the development of hypertension, albuminuria, or frank edema. She should receive at least the protein intake as recommended by The Technical Commission of The Health Committee on Nutrition for the League of Nations, 1.5 to 2.0 Gm. of protein per kilo, or for the 132-pound female, 90 to 120 Gm. Since much of the protein in the average diet is plant-borne, and therefore certainly less efficient, it is probable that an arbitrary figure of 150 Gm. of protein is more satisfactory, of which 110 Gm. should be as animal protein. The carbohydrate of the diet should be close to normal, namely, 300 to 350 Gm. Fat should be low, from 55 to 60 Gm. The diet should be low in sodium chloride (2 Gm. daily or less), high in calcium and potassium by virtue of a liberal milk allowance, and should meet Sherman's optima for vitamins. Vitamin D and the vitamin B complex will to advantage be added. Such a diet will range between 2,295 and 2,540 calories (Table I).

A diet of this sort will not favor water retention, will adequately glycogenize the liver, will tend to prevent hypercholesteremia, will supply unsaturated fatty acids so essential to the economy of all human beings, will furnish adequate protein for building the tissues of gestation, or for stimulating a sluggish metabolism through its specific

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

STILLBIRTHS AND NEONATAL DEATHS*

SCOTT C. RUNNELS, M.D., AND BURDETT WYLIE, M.D., CLEVELAND, OHIO

INTEREST has been centered on the problem of maternal mortality and the conservation of the older child to such an extent that the losses of babies at and shortly after birth have been largely neglected. The sources for this study are the various reports of the Bureau of the Census and monthly reports sent by a group of 46 hospitals to the Hospital Obstetric Society of Ohio.

The first problem is one of definition, as the terms stillbirth and neonatal death are indefinite and have different interpretations. The Census Bureau points out that the meaning of stillbirth is fixed by law in 25 states, by ruling of the State Board of Health in 22, by the local registrars in Pennsylvania, and by a letter defining the term to the doctors in Maryland. In the 25 states in which the definition is fixed by law, the term "advanced to the fifth month" is used in 21, with the exception that in the City of New York any product of conception is required to be registered, although the state legally defines the term as "advanced to the fifth month." The four states that are out of line are Connecticut which defines a stillbirth as a conception of "not less than twenty-eight weeks," in the District of Columbia the law is "passed the fifth month," in Indiana "seven months and over" and in the State of Washington "beyond the seventh month."

It would simplify the matter if the four states whose laws are not in accord with those of the 21 would amend their statutes. The situation is much simpler in the other 24 states. Here, merely an alteration in the ruling of the Board of Health would suffice. Delaware and New Hampshire have no definite ruling, Maryland and Missouri consider any dead product of conception a stillbirth, Idaho reports at four months, Kentucky, Ohio, and Massachusetts at four and one-half months, Montana and Pennsylvania after the fourth month, Maine, New Jersey, South Carolina, Vermont, Virginia, Wyoming at five months, Wisconsin after the fifth month, Nevada and Utah six months, Rhode Island after the sixth month, Kansas past the twenty-eighth week, and North Dakota does not report stillbirths until the seventh month. Any interpretation of stillbirth statistics must bear in mind the source of the material before evaluation.

The term neonatal deaths is also indefinite, being defined as "death in the newborn." As commonly used it means the death of the baby before the mother has left the hospital. In the reports from Ohio hospitals, given later in this paper, it is used in this sense. This is the most likely time of death, and while the time of hospital stay is indefinite, it would probably be prolonged if the child showed any reason for anxiety. However, that definition will not be practical in studying cases taken from statistical tables, so for the cases analyzed from the Census Bureau reports we have considered deaths in the first month as neonatal. Infant mortality includes all deaths within the first year. The purpose of this study is to bring into clearer definition the essential differences between deaths occurring shortly after birth and those occurring later.

Turning now to the number of stillbirths and neonatal deaths occurring in the United States, we find that in 1937 for every 1,000 live births there were 33.4 stillbirths and 33.3 deaths within the first month. Or stated another way, out

*Read at the Annual Meeting of the Hospital Obstetric Society of Ohio, Columbus, Ohio, April 3, 1940.

- 543, 1933. (6) *Strauss, M. B.* (Boston): *Am. J. M. Sc.* 190: 811, 1935. (7) *Ashe, B. I., and Mosenthal, H. O.*: *J. A. M. A.* 108: 1160, 1937. (8) *Strauss, M. B.*: *Am. J. M. Sc.* 194: 772, 1937; 195: 516 and 723, 1938; 196: 188, 1938. (9) *Dodge, E. F., and Frost, T. T.*: *J. A. M. A.* 111: 1898, 1938. (See discussion by Addis, T.) (10) *Harden, Boyd*: *A Study in Pre-Eclampsia and Eclampsia*, 1936, University of Pittsburgh. (11) *Alvarez, R. R. D.*: *AM. J. OBST. & GYNEC.* 39: 476, 1940; *Newburgh, L. H., and MacKinnon, F.*: *Practice of Dietetics*, New York, 1934, The Macmillan Co., Chap. XII. (12) *McPhail, F. L.*: *J. A. M. A.* 111: 1894, 1938. (13) *Farr, Smadel*: *Proc. Soc. Exper. Biol. & Med.* 36: 472, 1937; *Howard*: *J. A. M. A.* 109: 1654, 1937. (14) *Cameron, J. D. S.*: *Ibid.* 113: 520, 1939. (15) *Reutmann, McCann*: *J. Clin. Investigation* 11: 973, 1932. (16) *Rabinowitch, I.*: *J. Nutrit.* 16: 549, 1938. (17) *Best, C. H., and Campbell, J.*: *J. Physiol.* 92: 91, 1938; 94: 47, 1938. (18) *Best, C. H.*: *Lancet* 1: 1155, 1934. (19) *Althusen*: *J. A. M. A.* 100: 1163, 1933. (20) *Young*: *J. Obst. Brit. Emp.* 26: 1, 1914. (21) *Hartman, F. W.*: *J. Obst. Brit. Emp.* 34: 279, 1927 (Discussion of Paper 2). (22) Personal experience of writer—a case in which blood urea before death reached 7 mg. per cent. (23) *Beaver, D. C., and Pemberton, J. deJ.*: *Ann. Int. Med.* 7: 687, 1933. (24) *Silver, S.*: (Review of Simmonds' Disease) *Arch. Int. Med.* 51: 175, 1933. (25) *Goodall, J. R.*: *AM. J. OBST. & GYNEC.* 26: 560, 1933. (26) *Hofbauer*: *Abst. AM. J. OBST. & GYNEC.* 37: 903, 1939. (27) *Teel, H. M., and Reid, D. E.*: *Endocrinology* 24: 297, 1939. (28) *Gilman, A., and Goodman, L.*: *J. A. M. A.* 109: 1545, 1937; *J. Physiol.* 90: 113, 1937. (29) *Anselmino, K. J., and Hoffmann, F.*: *Klin. Wchnschr.* 10: 1438, 1931. (30) *Dieckmann, W. J., Michel, and Woodruff*: *AM. J. OBST. & GYNEC.* 36: 408, 1938. (31) *Best, C. H., and Rideout, J. H.*: *Am. J. Physiol.* 122: 67, 1938; *Ann. Rev. Biochem.* 8: 349, 1939. (32) *Taylor, H. C., and Scadron, E. N.*: *AM. J. OBST. & GYNEC.* 37: 963, 1939. (33) *Herrick, W. N., and Tillman, A. J. B.*: *Ibid.* 31: 822, 1936; *Arch. Int. Med.* 55: 643, 1935. (34) *Zimmermann, H. M., and Peters, J. P.*: *J. Clin. Investigation* 16: 397, 1937. (35) *Goldblatt, H.*: *Bull. New York Acad. Med.* 14: 523, 1938; *Ann. Int. Med.* 11: 69, 1937. (36) *Wood, J. E., Jr., and Nix, H.*: *J. A. M. A.* 110: 332, 1938. (37) *Peters, J. P.*: *Ibid.* 110: 329, 1938.

451 CLINTON AVENUE

Books Received

COMPLETE GUIDE FOR THE DEAFENED. By A. F. Niemoeller. 256 pages. Harvest House, New York, 1940.

HANDBOOK OF HEARING AIDS. By A. F. Niemoeller. 156 pages. Harvest House, New York, 1940.

IMMUNE BLOOD THERAPY OF TUBERCULOSIS. By Joseph Hollos, M.D. 195 pages. Bruce Humphries, Inc., Winchester Street, Boston, Mass.

BIOCHEMISTRY OF DISEASE. By Meyer Bodansky, M.D., and Oscar Bodansky, M.D. 684 pages. The MacMillan Company, New York, 1940.

DIE GEBURTSHILFLICHEN OPERATIONEN. Ihre Ausfuehrung und Anwendung. Von Professor Dr. med. Heinrich Martius, Direktor der Universitaets-Frauenklinik Goettingen. Second revised edition, with 281 illustrations, part in color. 286 pages. Verlag von Georg Thieme, Leipzig, 1940.

SEX IN MARRIAGE. By Ernest R. Groves and Gladys Hoagland Groves. New revised edition. 250 pages. Emerson Books, Inc., New York, 1940.

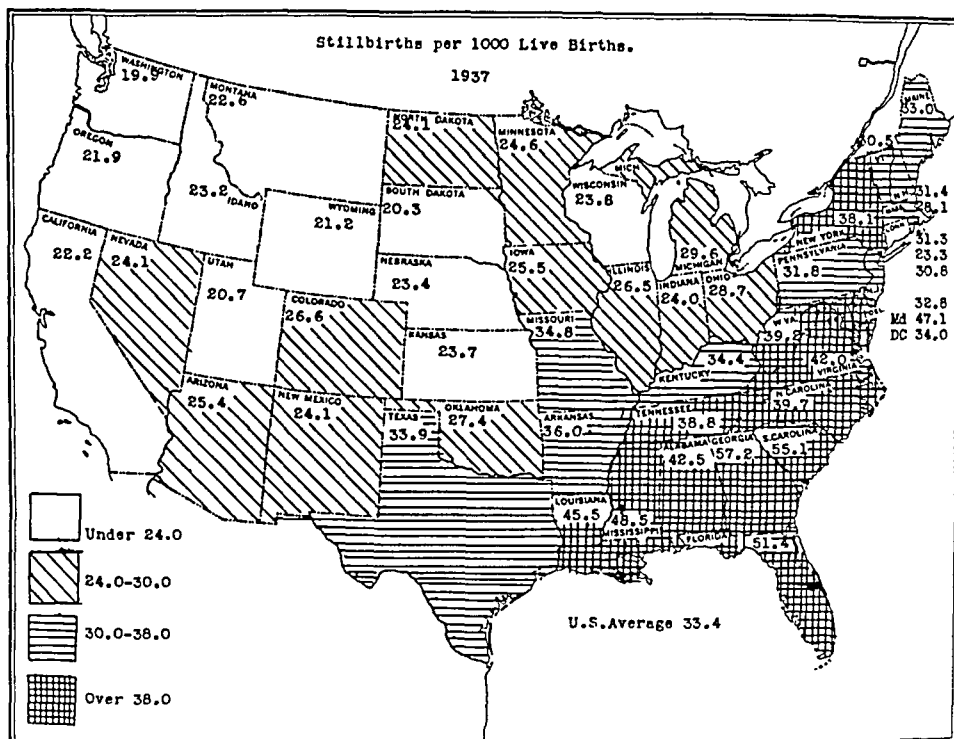


Chart 1.

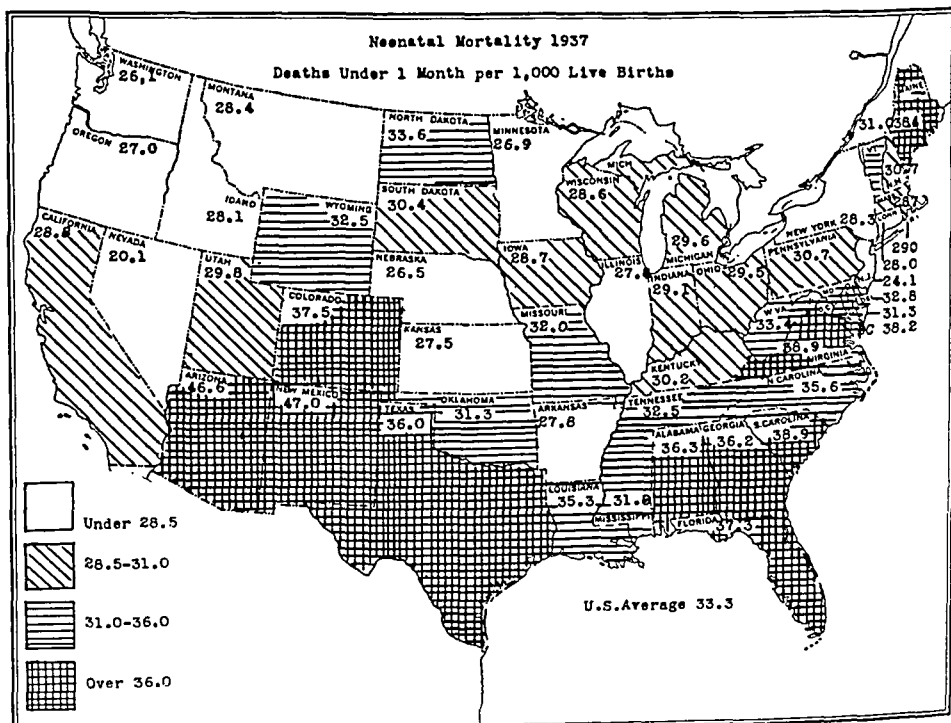


Chart 2.

of every 100 pregnancies that approach term, there is a loss of 6.45 per cent of the babies before the end of the first month. The distribution of these losses by states is pictured in Charts 1 and 2. Stillbirths have decreased from 86,466 in 1930 with a rate of 39.0 per 1,000 live births, to 73,467 in 1938 with a rate of 32.0. Neonatal deaths have fallen in number from 78,182 in 1930 with a rate of 35.7 per 1,000 live births to 73,311 in 1937 with a rate of 33.3. The distribution of these improvements by states is shown in Charts 3 and 4. The general improvement in infant mortality has been shown by the Children's Bureau in their publications. This demonstrates that there has been greater improvement in child care in the cities than in the rural districts.

Segregating the infant deaths occurring in the first month of life we find that the improvement in infant mortality in the later months has been greater than that in the first month.

Distributing infant deaths according to the time following birth at which they occur it becomes apparent that the longer the child lives the more chance it has of continuing to live. There are more deaths in the first day following birth than there are in the rest of the first week and more deaths in the first week than there are in the last eleven months of the first year.

The distribution of stillbirths according to the month of gestation cannot be done so satisfactorily from a statistical point of view because of the irregularity of reporting stillbirths. However, the data in Table I were taken from figures reported by the Census Bureau from 7 states and 2 cities for the years 1935 and 1936. Of the states Connecticut and Washington report stillbirths only after

TABLE I. STILLBIRTHS BY MONTH OF GESTATION IN SEVEN STATES AND TWO CITIES

Connecticut, Illinois, New Jersey, New York, Oregon, Washington, Baltimore,
and District of Columbia
1935-1936

Under 4 months	737	2.4%	
4 Months	1,381	4.5%	
5 Months	2,526	8.2%	
6 Months	3,397	11.0%	
7 Months	4,335	14.0%	40.1%
8 Months	7,031	22.8%	
9 Months	9,237	29.8%	52.6%
10 Months and over	247	0.8%	
Unknown	2,007	6.5%	
	30,898		

seven months; the rest fall in the group reporting in the fifth month. Re-classifying the same cases on the basis of reasons for death, we will take the longer list given by the Census Bureau of the cause for these stillbirth deaths and regroup them on an etiologic basis. For comparison we also list the fewer stillbirths derived from the reports of the Ohio hospitals for the year 1938.

With a few exceptions there is a fairly close analogy between the figures presented by the Ohio Hospitals and those of the Census Bureau. The two notable exceptions are the headings "death in utero" and the indefinite group in both of which the matter of classification could well have bearing. It is not to be expected that any really definitive classification can be arrived at until a fairly large number of cases in which autopsies have been done are accumulated. It has been the experience of the authors that several inexplicable intrauterine deaths have been found to be due to such causes as antepartum fetal pneumonia, and asphyxia has been found to be a congenital absence of the trachea. The Census reports can be no more accurate than are the death returns filed by the attending physicians. However, from year to year the accuracy of the returns is improving and the analogy between the more definite causes in the two lists published is close enough so that they are mutually confirmatory.

In an effort to evaluate the various "probable causes of death" we proceed now with some further detailed data from the Ohio reports. It is fair to assume, considering the close correlation of Table II, that these figures are probably a fair sample of the entire United States. Total births in series were 39,821. In contrast to these figures which include only those infants whose deaths were due to prematurity, we have Table IV showing deaths from all causes arranged on the basis of fetal age. Not only is the mortality greater in earlier cases of prematurity but the ratio of stillbirths to neonatal deaths is higher.

It will be noted that in a considerable group of cases the method of delivery was not stated, hence the above percentages tend to be lower than the true figures. The interesting relationship between the deaths following spontaneous and forceps deliveries can of course be readily explained by the fact that practically all prema-

TABLE II

	CENSUS BUREAU			OHIO HOSPITALS	
Deaths due to dystocia		4,493	14.5%	127	11.9%
Breech presentation	764				
Other malposition	550				
Traumatism	632				
Deformed pelvis	359				
Other difficult labors	2,188				
Prolapse and compression of cord		3,343	10.8%	119	11.2%
Toxemia and albuminuria		2,260	7.3%	118	11.1%
Premature separation of placenta		2,207	7.1%	91	8.6%
Placenta previa		865	2.8%	30	2.8%
Death in utero (macerated 545)		1,807	5.8%	172	16.2%
Malformation		1935	6.3%	85	8.0%
Syphilis		666	2.2%	23	2.2%
Indefinite		4,393	14.2%	50	4.7%
Asphyxia, etc.	2,298				
Diseases of membranes	1,473				
Other specified cause	622				
Cause not specified	(6,662)	8,931	29.0%	249	23.3%
Abortion, etc.	2,269				
		30,900	100.0%	1,064	100.0%

TABLE III. PREMATURE BIRTH AS "THE PROBABLE CAUSE OF DEATH"

	NO. CASES	STILLBIRTHS	NEONATAL DEATHS	TOTAL DEATHS	MORTALITY
Prior to seventh month	319	87 (27.4%)	118 (37.0%)	205	64.4%
Seventh month	713	50 (7.0%)	171 (24.0%)	221	31.0%
Eighth month	696	8 (1.1%)	54 (7.8%)	62	8.9%
	1,728	145 (8.4%)	343 (19.9%)	488	28.3%
Incidence of prematurity 4.35 per cent					

TABLE IV. STILLBIRTHS AND NEONATAL DEATHS ACCORDING TO FETAL AGE

	NO. CASES	STILLBIRTHS	NEONATAL DEATHS	TOTAL DEATHS	MORTALITY
Prior to seventh month	319	185 (58.0%)	134 (42.0%)	319	100.0%
Seventh month	713	154 (21.6%)	232 (32.5%)	386	54.1%
Eighth month	696	117 (16.7%)	128 (18.4%)	245	35.1%
	1,728	456 (26.4%)	494 (28.6%)	950	55.0%
Term and not stated	38,093	608 (1.6%)	348 (0.9%)	956	2.5%
Total	39,821	1,064	842	1,906	

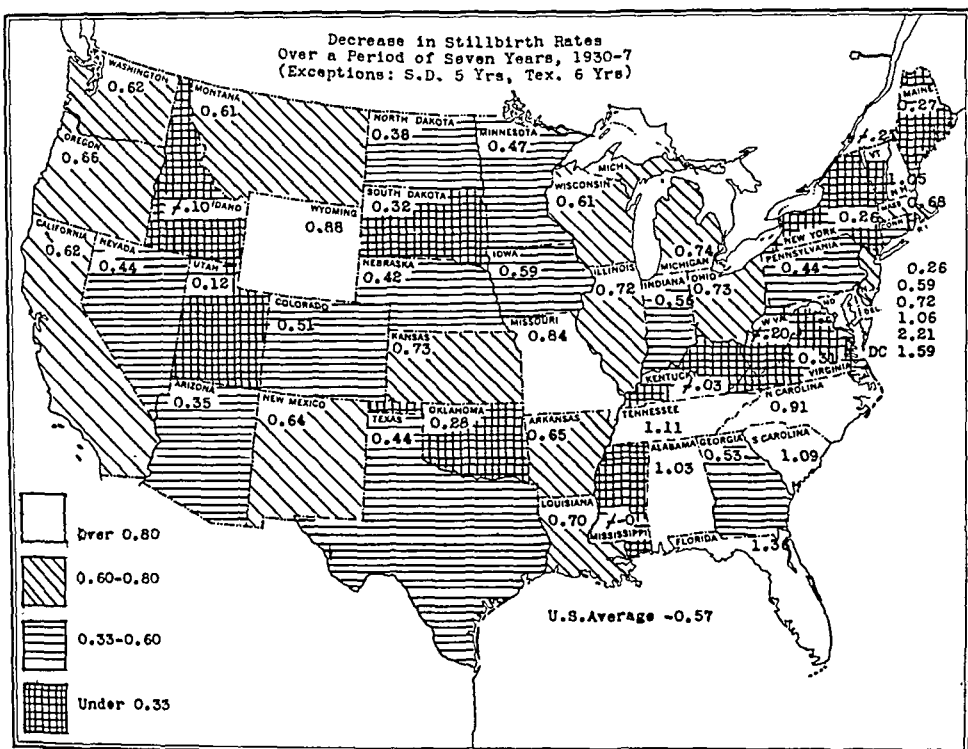


Chart 3.

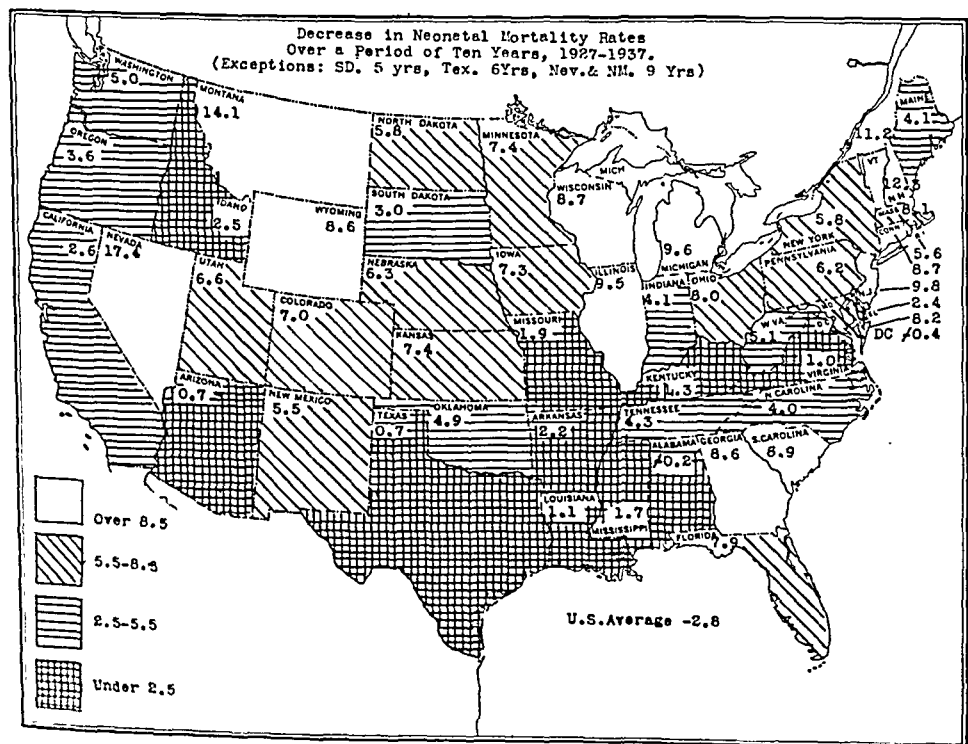


Chart 4.

the major causes are listed, the others being grouped under the heading "all other causes." However, no cause is excluded that had as many as 1,000 deaths in the first twelve months.

TABLE IX. MAJOR CAUSES OF INFANT DEATH. UNITED STATES, 1930, 1936, AND 1937

	IN FIRST MONTH			IN LAST ELEVEN MONTHS		
	1930	1936	1937	1930	1936	1937
Prematurity	35,290	32,452	32,524	1,466	1,191	1,133
Birth injury	10,475	9,502	9,496	151	148	102
Malformation	8,551	7,296	7,138	3,196	3,124	3,031
Debility	3,301	2,748	1,919	2,283	1,759	1,561
Pneumonia	3,440	2,972	2,990	12,749	14,775	13,577
Diarrhea	1,849	1,556	1,443	15,443	11,794	11,203
Influenza	366	419	493	2,459	3,082	3,226
Whooping cough	187	91	155	3,191	1,627	3,016
Syphilis	775	688	698	1,035	886	824
External cause	639	662	543	1,704	1,943	1,838
Unknown	5,222	4,269	3,990	3,582	2,704	2,667
All other causes	8,562	7,214	7,498	16,497	9,443	8,866
Total	78,657	69,869	68,887	63,756	52,476	51,044
Total births	2,233,958	2,144,798	2,203,337			
Rate per 1000	3.56	3.25	3.12	2.89	2.44	2.31

Several points are apparent. First, the figures on neonatal deaths have not made as marked an improvement as have the deaths in the later months. Second, the chief reasons for neonatal deaths are prematurity, birth injury, and malformation, in all of which the improvement has not been marked, and in which it cannot be expected that great savings could be made. Third, the great improvement in the deaths of later months has been in the infectious diseases, but even here those diseases that come in epidemics, pneumonia, influenza, and whooping cough, do not show constant decrease. While there should be continued improvement in the number of neonatal deaths, it cannot be expected to be as great as the improvement in the later months.

There are two factors, sex and race, that have a distinct bearing on infant deaths. Male babies die more frequently than female; this is true before as well as after birth.

TABLE X. EXCESS OF BIRTHS AND DEATHS OF MALE INFANTS. FIGURES TAKEN FROM THE CENSUS BUREAU STATISTICS FOR THE YEARS 1935, 1936, AND 1937. THE TOTAL BEING DIVIDED BY 3 TO PRODUCE THE ANNUAL AVERAGE

	LIVE BIRTHS	STILLBIRTHS (WHEN SEX REPORTED)	DEATHS DURING FIRST YEAR
Male	1,109,857	41,724	68,909
Female	1,054,449	32,559	51,959
Excess of males	55,408	9,165	16,950

Ratio of deaths by end of first year: male 3.97; female 3.00.

Of total pregnancies approaching term (sum of live and stillbirths) the death rate by end of first year is: male 95.5 per 1000; female 77.5.

Of total pregnancies approaching term male excess is 64,573
By end of first year excess of male deaths is 26,115 40.4%

Excess of males at end of first year reduced to 38,458

No explanation of these facts is presented, but the difference is very striking. The factor of race is worthy of discussion. Both the stillbirth and the infant mortality rates are considerably increased because of the large number of infant

TABLE V. MATERNAL DISEASE IN RELATION TO DEATH OF CHILD

	NO. CASES	STILL- BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	MORTALITY
Toxemia (Incidence 2.53%)	1,004	122	38	160	15.9%
Diabetes	23	4	6	10	43.5%
Syphilis	?	19	15	34	?

TABLE VI. FETAL DISEASE AS CAUSE OF DEATH

	NO. CASES	STILL- BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	MORTALITY
Malformations (Incidence 1.35%)	535	85	113	198	37.1%
Erythroblastosis	25	3	9	12	48.0%
Enteritis	33	×	15	15	45.5%
Hemorrhagic disease of newborn	18	×	10	10	55.6%
Pneumonia	31	×	18	18	58.0%

TABLE VII. DISTRIBUTION OF INFANT DEATH BY METHOD OF DELIVERY

DELIVERY	NO. CASES	STILLBIRTHS	NEONATAL DEATHS	TOTAL DEATHS	MORTALITY
Forceps	18,070	174 (0.96%)	161 (0.89%)	335	1.85%
Spontaneous	18,482	404 (2.18%)	311 (1.67%)	715	3.85%
Cesarean section	947	48 (5.08%)	47 (4.95%)	95	10.03%
Pod. version	769	62 (8.09%)	35 (4.56%)	97	12.65%
Breech	1,456	111 (7.62%)	96 (6.59%)	207	14.21%
Craniotomy	19	19 (100%)		19	100.00%
Post mortem cesarean sec- tion and other opera- tions	78	5	2	7	
Not stated		241	190	431	
Total	39,821	1,064 (2.69%)	842 (2.12%)	1,906	4.81%

tures, which contribute almost 58 per cent of the babies lost, are delivered spontaneously. On the other hand a great many forceps deliveries are purely elective and add no serious risk to the child.

In an effort to arrive at the relative incidence of fetal loss due to birth accidents in the various methods of delivery, an analysis of births at term where death was attributed to asphyxia, birth injury, or dystocia was made. This showed spontaneous delivery to have the lowest percentage incidence of fetal death (stillbirth and neonatal combined). Considering the incidence of death in spontaneous delivery as one, deaths following other delivery methods appeared in ratios as shown in Table VIII.

Returning to the Census Bureau reports we will consider the causes of infant deaths. Table IX lists all the deaths reported for the years 1936 and 1937, the latest at present available, compared with the deaths for the year 1930. Only

TABLE VIII. RATIO OF DEATH FROM INJURY BY METHOD OF DELIVERY

Spontaneous	1.0
Forceps	1.7
Cesarean section	6.6
Breech	8.3
Podalic version	16.8

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Gynecologic Operations

Chavannaz, J.: Reflections on Vaginal Hysterectomy, *Rev. franç. de gynéc. et d'obst.* 33: 877, 1938.

Today vaginal hysterectomy has almost fallen into oblivion. In fact there are well-known surgeons who have not performed a single one of these operations and many surgeons have not even seen one done. Chavannaz discusses vaginal operations from his experience of twenty years.

There is no doubt that a vaginal hysterectomy can be performed much more rapidly than an abdominal hysterectomy. It can be done in eight to ten minutes and even less time. The risk of infection during the operation is certainly less than in cases of abdominal hysterectomy. If an infection does take place, drainage readily occurs and there is very little danger of general peritonitis. There is no postoperative scar and this is advantageous from an esthetic point of view.

The author favors the use of clamps and not ligatures. The clamps are left in place for forty-eight hours. His indications for the operation are as follows: prolapse of the uterus, small fibroid uteri and cases of metritis where radiotherapy is not advisable and certain cases of uterine and uteroadnexal infection. If a plastic operation is necessary, it is performed about three months after the vaginal hysterectomy.

The author maintains that with proper indications and technique the postoperative convalescence is comparable to that following a curettement. He believes that about 5 per cent of all hysterectomies should be performed by the vaginal route.

J. P. GREENHILL.

Faure, J. L.: Vaginal Hysterectomy, *Bull. Soc. d'obst. et de gynéc.* 27: 45, 1938.

During the past twenty-five years Faure has attempted to teach the technique of vaginal hysterectomy to his students. In spite of this, fewer of these operations are being performed. The author's chief indication for vaginal hysterectomy is infection of the uterus, because the vaginal route offers an excellent route for drainage. He has for many years advocated this operation for cases of puerperal infection in spite of the opposition of all obstetricians and many surgeons. The operation is also indicated in women who are exhausted, sometimes nearly dying, and in obese women. The operation is very well tolerated by all patients even when it takes a long time to complete. Where there are no complications, the operation requires only a few minutes. However, this is no reason to extend the indications to many other conditions such as extensive prolapse of the uterus except where there are serious pathologic changes in the uterus.

Faure believes that the simplest, cleanest, and most rapid technique of vaginal hysterectomy is Doyen's method of anterior hemisection. The only drawback of this operation is that it can be done only in cases where the uterus can readily be brought down. The operation can be done in five minutes.

J. P. GREENHILL.

Radford, Aubrey: Total Hysterectomy, *South African M. J.* 11: 232, 1937.

The view is presented that owing to the ease and safety of subtotal hysterectomy this procedure has been adopted too frequently and unjustifiably. The author pleads for a more widespread use of total hysterectomy via the vaginal route.

deaths occurring in the negro race. The stillbirth rate would be reduced from 33.3 to 29.2 if only the white stillbirths were taken into account. Considering negro births and stillbirths only, the rate is 63.2. Similarly the infant mortality rate is also affected. The 1938 rate for the United States is 51.0, the white rate being 46.0 and the negro rate 78.1. It is difficult to compare these rates state by state, because in many states there are few negro births, and where there are few births the rates lose in significance. However, of the states that have over 0.5 per cent of negro births a year, there are only four that have a negro infant mortality rate as low as the four states having the highest white rates. It is impossible to determine from these figures whether this poor record is inherent to the race, whether it is largely due to the type of care received by the negro, or whether it is due to the conditions under which he lives. There is much to argue against the first possibility in the fact that the white urban infant mortality in many of the southern states is very high. In fact in three of the states, the urban white infant mortality rate is worse than is the negro infant mortality for the same states (West Virginia, Alabama, and Mississippi). However, it is possible statistically to segregate the negro race and show that the large number of stillbirths and infant deaths which they contribute raise the average for the country considerably. It is more than possible that if certain other factors could be eliminated similar reductions could be expected.

SUMMARY

Attention is called to the marked discrepancies in the different states in the definition of the term "stillbirth," and a plea is made for conformity.

The definition of "neonatal death" is discussed. The number of stillbirths and neonatal deaths in the United States are analyzed with an attempt to fix the cause and age at occurrence.

The greater improvement in the later infant mortality over a period of years, as compared with the death rate of the newborn, is discussed.

The high incidence of death in negro babies is noted, and the higher mortality of male babies is demonstrated.

CONCLUSION

The considerable risk of deaths at the time of birth and shortly thereafter has been demonstrated. This risk is decreasing from year to year but not with great rapidity, because of the fact that some of the causes are not amenable to treatment. A better understanding of the factors involved may help to save many lives.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF APRIL 19, 1940

The following papers were presented:

The Coincidence of Tuberculosis of the Endometrium With Tuberculosis of the Lung. Drs. Julius E. Lackner, Walter Schiller, and Alex. S. Tulskey (by invitation). (For original article, see page 429.)

Effect of Vitamin K Administered to Patients in Labor. Drs. J. E. Fitzgerald and Augusta Webster (by invitation). (For original article, see page 413.)

Retrodisplacement of Uterus in Relation to Pregnancy. Dr. Albert H. Aldridge (by invitation). (For original article, see page 361.)

important for a correct diagnosis. However, pelvic puncture should not be used in acute cases, it should be reserved for subacute and chronic inflammatory tumors. Therapeutically the aspiration of the contents of inflammatory masses brings about a cure even if the entire contents of a cystic mass are not removed. For some reason, puncture of an inflammatory mass hastens absorption.

The author followed up a series of 301 women who had undergone a pelvic puncture for inflammatory masses at least five years previously. In 47 of these cases (15 per cent), pregnancy followed pelvic puncture and 31 of the women went to term. In 218 cases, complete cure resulted only in 36 cases, and in the others a second course of conservative therapy had to be instituted. Only 47 women had to be operated upon. These statistics support the author's contention of the great therapeutic value of pelvic puncture in cases where inflammatory masses are present.

In cases of pelvic abscess, the author advocates immediate incision and drainage of the cul-de-sac.

There are few dangers connected with pelvic puncture. In the series of more than 2,000 pelvic punctures performed in the author's clinic, the bowel was penetrated only between 20 and 30 times. This accident is entirely harmless. A more serious complication is bleeding, but this occurs almost exclusively if the puncture is made to one side instead of in the midline. However, nearly always the bleeding is external and can be controlled by packing the vagina or occasionally by using a suture. Intra-abdominal hemorrhage was never encountered. Another danger is rupture of a thin-walled abscess. This occurred once in this series. The author never saw an infection follow a pelvic puncture. Nevertheless he warns that this procedure should never be carried out in the office, but only in a place where a laparotomy may be performed if it should become necessary.

J. P. GREENHILL.

von Mihalkovics, E.: Simple Puncture as Palliative Therapeutic Treatment in Purulent Accumulations in the Female Pelvis, *Monatsschr. f. Geburtsh. u. Gynäk.* 109: 257, 1939.

In the opinion of the author, colpotomy should not be used when dealing with accumulations of pus in the adnexa because of the danger of subsequent fistula. This procedure is permissible only where death seems imminent. In cases of recent purulent inflammation the best treatment is aspiration of the pus by means of a syringe through the cul-de-sac. This simple procedure will bring about rapid improvement in three-fourths of all cases. It may also be carried out in cases of parametric abscesses and in infected hematoceles.

When there is an abscess in the cul-de-sac following salpingitis, a colpotomy should be performed because there is no danger of fistula formation. However, an incision is not necessary in these cases because aspiration gives just as good results.

J. P. GREENHILL.

Rubin, I. C.: Renal Tumor and Ectopic Kidney Associating or Simulating Uterine and Adnexal Tumor, *Urol. & Cutan. Rev.* 45: 626, 1939.

Six cases of renal tumor and 3 cases of ectopic kidney were encountered by Rubin on the Gynecological Service at Mt. Sinai Hospital in the past eleven years in a series of 2,065 laparotomies. In 6 of the 9 cases the renal pathology was associated with genital pathology. In 3 the tumors simulated but were not confused with genital tumors. There were 3 renal cysts and 3 Grawitz tumors, one of which involved the ovary of the same side. There were 3 cases of sacral kidney, all 3 being found on the left side of the pelvis.

The rather uncommon occurrence of renal tumors in combination with genital tumors makes the diagnosis of the former a matter for special investigation. The renal tumor or anomaly was not primarily suspected in 5 of the 9 cases. Only

Plastic operations may be performed at the same time. The remaining cervix, in the subtotal hysterectomy, is a constant menace as an infective focus and often becomes the seat of carcinoma.

The author finds lumbar anesthesia ideal for vaginal hysterectomy.

F. L. ADAIR AND S. A. PEARL.

Haultain: The Treatment of Pyosalpinx, J. Obst. & Gynacc. Brit. Emp. 46: 503, 1939.

This is a review of 84 cases of definite pyosalpinx, 54 cases being acute and 30 chronic; 22 were instances of tuberculous pyosalpinx. Of the 54 acute cases, 34 patients received conservative treatment; this, however, failed in 10 cases and an operation had to be undertaken.

Clinical cure occurred in 20 cases following conservative treatment alone, while two patients died, both being tuberculous.

Operation is advised in all cases in which conservative treatment fails or the patient has continued ill-health, is constantly miserable with pain or/and menorrhagia, is unable to work, to look after her household or even enjoy life on account of her pelvic condition; the operation generally indicated is hysterectomy with removal of both appendages.

Four cases of rupture or leak of a pyosalpinx were encountered, and there were 2 other cases in which at the operation the Fallopian tubes were found to be on the point of rupture; 3 of these patients died, and all would probably have been lost had not immediate operation been possible. Five deaths are recorded among the 30 patients operated upon, three from rupture or necrosis of the tubal wall, the other two being cases for which conservative treatment had been carried out too long before operation was done.

Results are given of 30 operations for chronic pyosalpinx, one death being recorded from embolism on the twenty-third day of an otherwise excellent convalescence. Details of the 22 tuberculous cases, including the late results, are given, 8 being acute and 14 chronic. Twenty patients were operated upon and the radical operation was performed in 13. Only one death is recorded in the operated cases, and this occurred in a patient who had mixed infection of gonococci and tubercle bacilli. There was no mortality in the cases which were purely tuberculous. The late results, up to seven years later, were found to be uniformly excellent in those treated radically, there being no apparent spread or exacerbation of tuberculosis elsewhere; whereas when some form of conservative operation was done, the health of 3 out of the 7 so treated was found to be adversely affected at a later date.

J. P. GREENHILL.

Schultz, W.: Pelvic Puncture, Zentralbl. f. Gynäk. 63: 213, 1939.

Schultz first describes the technique of this operation; then discusses the indications. The chief use for this diagnostic procedure is to diagnose a tubal pregnancy. From 1919 to 1938 pelvic puncture was used to verify the diagnosis in 345 cases of ectopic pregnancy in the Hamburg Woman's Clinic. In 287 additional cases, an operation for tubal pregnancy was performed without a preliminary pelvic puncture, and in 14 cases, the puncture failed to give the desired information.

With the exception of blood in the peritoneal cavity due to endometriosis or rupture of an ovarian cyst, the aspiration of blood at the time of a pelvic puncture is definite proof of an ectopic pregnancy. If the tubal pregnancy is unruptured, no blood will be obtained.

Another indication for a pelvic puncture is the presence of an undefinable tumor in the pelvis. In 54 such cases the puncture resulted in a correct diagnosis 45 times. The material obtained by aspiration was fixed in alcohol and sectioned.

In the presence of gynecologic peritonitis, pelvic puncture has both diagnostic and therapeutic value. When inflammatory adnexa are present, pelvic puncture is

Approximately 20 per cent of retroversions are congenital and occur in patients in whom the plane of the pelvic inlet lacks the normal incline. In such congenitally flat adult pelvis, retroversion is normal and may be considered compensatory for the existing deviation from the more common and normal orthopedic condition. The function of the pelvic planes is supportive since the pelvic organs are held in place by the ligaments, and defensive in that they serve to deflect intra-abdominal pressure. Either one or both of these functions may be deranged by: (1) trauma (most common), (2) developmental errors, and (3) disease.

Simple, uncomplicated retroversions are symptomless. When symptoms are present, they are caused by complicating conditions. The complaints in congenital retroversion are due to attitudinal strain in the sacroiliac joints and erector spinae and psoas muscles. Uterine retroversion is followed by uterine prolapse of varying degrees, and this in turn is followed by descent of the bladder, vaginal vault, and cystocele formation. Upon the basis of incomplete evacuation of bladder contents cystitis develops.

The author urges that the fundamental principles of pelvic mechanics underly any corrective procedure indicated regardless of the specific operative technique employed. He offers three guiding principles: (1) An uncomplicated retroverted uterus does not need to be operated upon. (2) A congenital retroversion is not a gynecologic but an orthopedic problem. (3) No pelvic operation for the restoration of an organ is complete unless all defective supports are restored to their original equilibrium.

ARNOLD GOLDBERGER.

Malfanti, Juan: A New Technic of Hysteropexy, *Bol. Soc. chilena de obst. y ginec.* 4: 275, 1939.

The essential features of the author's operation for the correction of retroversion and retrodisplacement involve a dissection into the broad ligament along a line just beneath the round ligament. The round ligament is divided midway between its uterine attachment and the internal inguinal ring. The free ends are overlapped sufficiently to bring the uterus into the desired degree of anteversion, and then sewed to each other. Complete peritonization is secured by enclosing the shortened round ligament within the dissected folds in the broad ligament.

In the discussion of the paper the chief objection made to the procedure was the likelihood of interference with the blood supply and consequent atrophy of the round ligaments with recurrence of the retrodisplacement. Malfanti's statistics appear favorable. The article is illustrated.

R. J. WEISSMAN.

Ward, Grant E.: Ox Fascia Lata for Reconstruction of Round Ligaments in Correcting Prolapse of the Vagina, *Arch. Surg.* 36: 163, 1938.

To Koontz (*Ann. Surg.* 83: 525, 1936) belongs credit for devising a practical method of preserving fascia lata of the ox, so that it can be kept in the operating room for immediate use as any other suture material.

Ward describes in detail how in 1933 he made use of such prepared ox fascia in forming duplicate round ligaments for lifting up the short vagina which had prolapsed subsequent to a total hysterectomy for early adenocarcinoma. The operation took almost two hours. Patient made a smooth recovery and in 1937 still is well and free of any pelvic or bladder symptoms. The writer suggests that possibly in the same manner, preserved fascia lata could be used for correction of retroversion of a heavy uterus or in building up a weak pelvic floor.

HUGO EHRENFEST.

by x-ray study aided by intravenous injection of a radiopaque solution or by retrograde pyelography or by both procedures was the renal origin of the tumor determined.

The tumors encountered were of unusually large size reaching down into the pelvis where they were confused with tumors of the uterus or the adnexa. The routine use of x-rays in conjunction with pyelography, a practice which the author has adopted for some years in all large abdominal tumor cases, has led to correct preoperative diagnosis in 5 of the 6 renal tumor cases. The method of removal in 4 was by the transperitoneal route.

The diagnosis of sacral kidney is clinically only conjectural, the guess as a rule proving wrong. It is established by laparotomy or by x-ray study. In this connection a flat plate is not always reliable. Retrograde pyelography, ureteral catheterization, and intravenous urography yield pathognomonic evidence.

J. P. GREENHILL.

Lapeyre, N. D., Estor, H., and Gros, C.: Mikulicz Drainage in the Treatment of Tuberculous Salpingitis, Bull. Soc. d'obst. et de gynéc. 27: 94, 1938.

In the service of the authors 22 patients with tuberculous salpingitis were operated upon. In the patients in whom they used a Mikulicz drain there was not a single case of persistent parietal fistula or a fecal fistula. In the literature the authors found reports of 98 patients treated by Mikulicz drainage alone. Among these patients there were 10 deaths, 9 uncomplicated cures, 8 temporary parietal suppurations, and 10 purulent fistulas which were spontaneously cured. These figures according to the authors do not indicate that Mikulicz drainage yields bad results but that tuberculous salpingitis is a grave disease. They strongly advocate the use of this type of drainage.

J. P. GREENHILL.

Barros, P.: The Baldy-Webster Operation by the Vaginal Route, Rev. de gynéc. e d'obst. 1: 261, 1939.

The author in general recommends the vaginal route for gynecologic operations. He describes the operation of round ligament shortening according to the technique of Professor Werner of Vienna. The description is made clear by the use of both black and white and colored drawings. In the article the author illustrates a special forceps designed by himself to facilitate grasping of the round ligaments.

MARIO A. CASTALLO.

Thalheimer and Contiades: Rupture of the Vaginal Scar after Hysterectomy, Gynéc. et obst. 35: 299, 1937.

The patient, 50 years old, was brought to the hospital with severe vaginal bleeding which had come on suddenly while she was at stool. A loop of small intestine was found prolapsed into the vagina. She had had a little bleeding a few days previously after coitus. Total hysterectomy had been performed twelve years previously. The rupture was repaired by the abdominal route with recovery. The authors discuss the literature of rupture of vaginal scars. Coitus appears to be the commonest cause.

J. P. GREENHILL.

Beasley, B. T.: Altered Mechanics of the Female Pelvic Structures, South. M. J. 31: 976, 1938.

The anatomic principles underlying the normal support of the female pelvic structures, and the mechanism whereby derangements occur, is briefly and concisely described.

cedure was employed and in which there was not seen a single instance of thrombosis of legs or pelvic veins and not a single fatal case of pulmonary embolism. In contrast to this there is a series of 2,463 gynecologic operations performed before elevation of the foot of the bed was practiced. In this group there were 81 cases of thrombosis and 22 deaths from pulmonary embolism. No other explanation for the improved results could be found by the author, because no other changes have been made in the hospital routine. Even the type of anesthesia had remained the same, namely, preliminary use of pernocton followed by ether inhalation. In the 500 cases, the foot of the bed was elevated immediately after operation and this position maintained for four days. Elevation of the legs assists in the return flow of blood to the heart.

J. P. GREENHILL.

Charbonnier, A.: The Method of Getting Patients Out of Bed Early After Gynecologic Abdominal Surgery, *Compt. rend. Soc. Franç de gynéc.* 8: 314, 1938.

The author is in favor of getting patients out of bed early following abdominal operations for gynecologic disorders. However, exceptions to this practice are women in shock and those with drainage, hemorrhage, hypertension, and tachycardia. Likewise women with cardiac abnormalities, cachexia, severe infection and bedridden patients should be kept in bed a sufficiently long time after operation.

Women who are to get out of bed early are first made to exercise in bed even before operation in order to activate the circulation. These exercises include deep respiration and movements of the arms and legs. They are carried out daily from the day of operation until the patient leaves the hospital. On the third day after operation the patient is assisted to sit on the edge of the bed for five to fifteen minutes. On the fourth day she is helped to a chair where she remains for fifteen to sixty minutes. On the fifth day she takes a few steps in the room and stays up for one to two hours. On the sixth day she remains up for two to four hours. On the following days the patient may walk around in the halls and may walk up and down stairs.

Among 285 women who underwent this routine, there was not a single accident and only one case of phlebitis.

J. P. GREENHILL.

Correspondence

To the Editor:

In reading obstetric literature, I am struck with the diversity of meanings attached to the words "parous, primipara," etc. The word "parous" is used by some to designate "one who has borne a child," by others to mean "one who is now pregnant," and by still others "one who has been delivered of a living child." Thus a nullipara may be a woman who has never been pregnant, or one who is in her first pregnancy but not yet delivered, or one who has had any number of miscarriages. A primipara may be a woman who is in her first pregnancy, or one who has completed her first pregnancy, or one who has had one completed pregnancy with a living or dead fetus, according to the use of the word parous, and is now in her second pregnancy, or one who has had any number of miscarriages plus one living infant and is now in another pregnancy, or one who has had any number of miscarriages and is now in another pregnancy. The number of combinations is practically unlimited, and all may be found in obstetric literature. One woman referred to by an author as "para iii" was in reality in her ninth pregnancy. She had previously had three living children and five miscarriages.

With such a wealth of confusion in terminology, it becomes apparent that in order to have one's meaning unmistakable, one must further define just how many

Decoulx, P. and Patoir, G.: Results of Conservative Surgery for Sclerocystic Oophoritis, Bull. Soc. d'obst. et de gynéc. 26: 82, 1937.

The authors review a series of 200 cases of sclerocystic oophoritis. In 165 cases the treatment consisted of total or partial resection of the ovaries and in 35 cases also a hysterectomy was performed. There were two deaths following operation, one from embolism and the other from postoperative hemorrhage. There were bad results in 53 per cent of the cases. These consisted of persistent pain, irregular and painful menstruation, and impossibility of leading a normal existence. Furthermore 25 per cent of these women had to have a second operation. Good results were obtained in 47 per cent of the cases and 10 per cent of these had one or more babies following their operation.

J. P. GREENHILL.

Hamant, A., Girard, G. and Soubiran: Two Cases of Residual Cysts After Hysterectomy, Compt. rend. Soc. franç. de gynéc. 8: 223, 1938.

The authors report two cases where ovarian cysts appeared after hysterectomy. They believe the predisposing cause of these cysts lies in the local conditions such as previous inflammation, hence these cysts are frequently found in women who have had drainage after operation. In both of the authors' cases, drainage had been used.

The patients return after hysterectomy because of pain or because they have observed abdominal swelling. In some women, the cyst is discovered accidentally.

Unusually these cysts appear within one or two years after hysterectomy but in the authors' second case it appeared nineteen years later.

These cysts cannot be prevented because even if both ovaries are removed there may be a supernumerary ovary left behind. Moreover a simple hematoma may become a cyst or an infection may lead to cyst formation.

If a cyst is found in a woman who is near the menopause, it may be advisable to wait for it to disappear spontaneously, or radiotherapy may be used. The treatment of choice, however, is laparotomy.

J. P. GREENHILL.

Knaus, Herman: A New Phenomenon Which Is an Accurate Indication for Surgical Interference in Peritonitis of Pelvic Origin, Klin. Wehnschr. 16: 963, 1937.

Knaus has observed, for the last five years, a new phenomenon which occurs exactly at the time when the infection reaches the general peritoneal cavity. It consists in the complete absence of all respiratory movements of the abdominal wall between the umbilicus and the symphysis. Such respiratory movements stop long before the general signs of abdominal peritonitis set in. When observed, therefore, this phenomenon is a definite indication for immediate drainage of the abdominal cavity. Such early drainage has enabled the author to save many lives which would have been lost, if operation had been delayed until the standard signs of generalized peritonitis had set in.

RALPH A. REIS.

Schmid, H. H.: Prevention of Postoperative Thrombosis and Embolism, Zentralbl. f. Gynäk. 61: 307, 1937.

At the meeting of the German Gynecological Society in 1935, it was reported that thrombosis and embolism could be prevented by the simple procedure of elevating the foot end of the bed after all extensive gynecologic operations. Now Schmid reports a series of 500 serious gynecologic operations in which this pro-

The leadership of medical schools in developing and guiding graduate training programs in these specialties is evidenced by the fact that all but 12 of the approved programs are in hospitals which have an affiliation with a medical school for graduate training purposes.

In only three instances is training in general surgery required in qualifying for appointment for graduate training in obstetrics and gynecology. It has also been unusual to find any exchange of residents between the departments of general surgery and obstetrics and gynecology in the hospitals that have been surveyed by the College. As the programs are at present formulated, in many hospitals little opportunity is provided for the future obstetrician and gynecologist to gain broad knowledge of some of the general surgical problems of the lower abdomen, or for the general surgeon in training to gain experience in gynecologic problems.

Three major types of basic science activity in graduate training programs in hospitals are recognized by the College; first, the practical study of surgical pathology; second, basic course—a more or less formal academic type of instruction; third, research. In 49 of the programs of training in obstetrics, gynecology, and the combined specialties, provision is made for practical study of surgical pathology; in 19 provision is made for a basic course, mostly on a part-time service arrangement; in 6, provision is made solely for research.

In obstetrics and gynecology, as in general surgery and the other surgical specialties, the objective of graduate training is the development of a surgeon having a thorough background of knowledge fundamental to his specialty and possessing skill in the techniques of his profession. One of the most important requisites of an effective program is a well-organized staff of exclusive specialists in their respective fields, having high scholastic and professional standing, and possessing the attributes of the teacher. Personal supervision and direction of the work of the resident staff by assigned personnel should obtain at all times. An outpatient department with systematic follow-up clinics is essential to a well-organized program. The resident staff should attend medical staff, departmental and clinicopathologic conferences, observe and participate in autopsies on the service, be responsible for some teaching activities, be directed in the study of the basic sciences and of scientific literature, and obtain sufficient operative experience under supervision to provide a reasonable degree of technical efficiency.

As a preliminary to a resident staff appointment, a candidate must be a graduate of an approved medical school and have had at least one year of internship in a hospital providing acceptable interne training.

A list of the plans approved by the College for training in obstetrics and gynecology, and the separate specialties combined, follows:

Hospitals Approved for Graduate Training in Obstetrics and Gynecology
By the American College of Surgeons

Los Angeles County Hospital Los Angeles, Calif.	University of Chicago Clinics Chicago, Ill.
Stanford University Hospitals San Francisco, Calif.	University Hospitals Iowa City, Iowa
University of California Hospitals San Francisco, Calif.	University of Kansas Hospitals Kansas City, Kan.
New Haven Hospital New Haven, Conn.	Louisville City Hospital Louisville, Ky.
Gallinger Municipal Hospital Washington, D. C.	Charity Hospital of Louisiana New Orleans, La.
Grady Hospital (Emory University Service) Atlanta, Ga.	Mercy Hospital Baltimore, Md.
University Hospital Augusta, Ga.	University Hospital Ann Arbor, Mich.
Presbyterian Hospital Chicago, Ill.	Grace Hospital Detroit, Mich.
Research and Educational Hospitals of the University of Illinois Chicago, Ill.	Harper Hospital Detroit, Mich.
	Henry Ford Hospital Detroit, Mich.

pregnancies the woman has had if she is described as "para ii" for example. If such elaboration is necessary to make the use of the word "para" clear, would it not be preferable to leave out the "para ii" and let the explanation suffice? Thus a woman would not be "para i, para iii, or para ix," but she would be in her first, third, or ninth pregnancy, with so many miscarriages and so many living infants. Some writers will object that "para" is sanctioned by tradition, and should not be abandoned. It would appear impossible, however, to settle upon a meaning which would be adhered to by all writers. And is it worth while to continue the use of terms which are so obscure that at least two and perhaps a dozen meanings may be read into them? The purpose of scientific literature is to set forth a meaning that cannot be misunderstood, and of which there can be only one interpretation. No matter how hallowed the tradition, if it is obscure, it should be abandoned. It would be well if all obstetric texts and journals were to adopt a simple terminology, and if all medical students were to follow it, whereby a woman is described as "being in her first, or third, or ninth pregnancy," with all reference to "para" omitted. If this policy were adopted, the reader who is interested in the number of pregnancies which a mother has undergone who herself shows some condition attributable to childbearing, or who produces some malformation in her offspring thought to be dependent upon the number of times the mother has been pregnant, such a reader would have definite data for his study. At present, confusion in the mind of the reader, on such a simple matter as the number of pregnancies a patient of a colleague has undergone, is unavoidable.

MADGE THURLOW MACKLIN, A.B., M.D., LL.D.

University of Western Ontario Medical School, London, Canada.
August 10, 1940.

Items

Obstetrics and Gynecology in the Graduate Training Program of the American College of Surgeons

Of the 179 hospitals on the list approved for graduate training in general surgery and the surgical specialties by the American College of Surgeons, 73 have a program of training in either obstetrics or gynecology, or both, or the combined specialties. Those offering acceptable training in obstetrics number 12, in gynecology 8, and in obstetrics and gynecology 53. In training under approved programs are approximately 53 men in obstetrics, 19 in gynecology, and 234 in obstetrics and gynecology. Annually, 16 obstetricians complete two years, 3 complete three years, and 1 completes four or more years of training; 5 gynecologists complete two years, 2 complete three years, and 1 completes four or more years of training. For the combined specialties, 91 men are turned out each year, 84 of whom have had three years' training and 7 have had four or more years.

Affiliations with medical schools exists in the cases of 8 hospitals offering graduate training in obstetrics, 6 offering graduate training in gynecology, and 48 offering training in obstetrics and gynecology.

The graduate training committee of the College has felt it necessary to limit the approved list to hospitals where graduate training plans of three years for obstetrics and gynecology already existed or where immediate extension to three years was contemplated. When the training has been of particular excellence, a few exceptions to this rule have been made. However, when the training is for obstetrics or gynecology alone as separate specialties, it seems to be indicated that two years is considered acceptable.

The figures for approved training programs indicate the definite trend in recent years to combine these specialties, both from the educational standpoint and for the development of combined services in many medical schools and hospitals.

American Board of Obstetrics and Gynecology

The annual written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

The following action regarding case records to be submitted by candidates taking the Group B, Part I, examination was passed by the Board at its annual meeting in Atlantic City, N. J., on June 6, 1940: "Case records submitted by candidates must be of patients treated within four years prior to the date of the candidate's application. The number of cases taken from one's residency service should not be more than half (25) of the total number of fifty (50) cases required."

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's Office not later than October 5, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, immediately prior to the June, 1941, meeting of the American Medical Association.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Training Requirements

In response to numerous inquiries regarding special training requirements, the Board desires again to announce that there are three methods of meeting these requirements for admission to the Board examinations. First, by the residency system; second, by the partial residency and partial assistantship method; and third, entirely by the assistantship or "preceptorship method." Details of the residency requirements are given in the Board booklet. The Board will accept in lieu of the formal residency service the training acquired by a candidate serving on an assistant or dispensary staff of an obstetrical and gynecological division of a recognized Hospital, under the direction of a recognized obstetrician-gynecologist (preferably a Diplomate). The time required for this type of training must be longer than with the formal, more intensive residency type of training, and the allowance of time depends upon the duties and responsibility given the candidate. Applicants lacking all formal special training should have a minimum of five years of hospital clinic, or assistant staff appointments in the specialty, under approved direction. Teaching appointments without accompanying hospital staff or clinical appointments will not satisfy the Board requirements. A special form amplifying the original application must be filled out to cover the details of such assistantship, or preceptorship type, of training. The Board approves for special training, work done in institutions approved jointly by the Board and by the Council on Medical Education and Hospitals of the A. M. A.

PAUL TITUS, SECRETARY.

1015 Highland Bldg., Pittsburgh, Pa.

Central Association of Obstetricians and Gynecologists

The twelfth annual meeting will be held at the Hotel Lincoln, Indianapolis, Ind., on October 10, 11, and 12, 1940. The guest speaker will be Dr. Robert Meyer, now of Minneapolis. The meeting is open to all physicians, without any registration fee.

Receiving Hospital
Detroit, Mich.
Woman's Hospital
Detroit, Mich.
Minneapolis General Hospital
Minneapolis, Minn.
University of Minnesota Hospitals
Minneapolis, Minn.
Mayo Foundation for Medical Education
and Research
Rochester, Minn.
Anker Hospital
St. Paul, Minn.
Firman Desloge Hospital
St. Louis, Mo.
St. Louis City Hospital
St. Louis, Mo.
St. Louis Maternity Hospital
St. Louis, Mo.
Kings County Hospital (Kings County
Division and Long Island Col-
lege Division)
Brooklyn, N. Y.
Long Island College Hospital
Brooklyn, N. Y.
Edward J. Meyer Memorial Hospital
Buffalo, N. Y.
Bellevue Hospital (Third Surgical Divi-
sion)
New York, N. Y.
Flower and Fifth Avenue Hospitals
New York, N. Y.
Lying-in Hospital
New York, N. Y.
Metropolitan Hospital
New York, N. Y.
Presbyterian Hospital
New York, N. Y.

Hospitals Approved for Graduate Training in Obstetrics

Touro Infirmary
New Orleans, La.
Baltimore City Hospitals
Baltimore, Md.
Johns Hopkins Hospital
Baltimore, Md.
Sinai Hospital
Baltimore, Md.
University Hospital
Baltimore, Md.
Boston Lying-In Hospital
Boston, Mass.

Hospitals Approved for Graduate Training in Gynecology

Johns Hopkins Hospital
Baltimore, Md.
University Hospital
Baltimore, Md.
Free Hospital for Women
Brookline, Mass.
Albany Hospital
Albany, N. Y.

Woman's Hospital
New York, N. Y.
Strong Memorial Hospital
Rochester, N. Y.
Duke Hospital
Durham, N. C.
City Hospital
Cleveland, Ohio
St. Luke's Hospital
Cleveland, Ohio.
University Hospitals of Cleveland
Cleveland, Ohio
University of Oklahoma, State Univer-
sity Hospital
Oklahoma City, Okla.
University of Oregon Medical School
Hospitals and Clinics
Portland, Ore.
Hospital of the University of Pennsyl-
vania
Philadelphia, Pa.
Jefferson Medical College Hospital
Philadelphia, Pa.
Kensington Hospital for Women
Philadelphia, Pa.
Elizabeth Steel Magee Hospital
Pittsburgh, Pa.
Vanderbilt University Hospital
Nashville, Tenn.
Baylor University Hospital
Dallas, Texas
State of Wisconsin General Hospital
Madison, Wis.
Toronto General Hospital
Toronto, Ont., Canada
Royal Victoria Hospital
Montreal, Que., Canada

Massachusetts Memorial Hospitals
Boston, Mass.
Margaret Hague Maternity Hospital
Jersey City, N. J.
Cincinnati General Hospital
Cincinnati, Ohio
John Gaston Hospital
Memphis, Tenn.
Medical College of Virginia
Richmond, Va.
University of Virginia Hospital
University, Va.

Buffalo General Hospital
Buffalo, N. Y.
Mount Sinai Hospital
New York, N. Y.
Graduate Hospital of the University of
Pennsylvania
Philadelphia, Pa.
John Gaston Hospital
Memphis, Tenn.

tions, thus bearing in mind the varying needs of the specialist as well as the general practitioner. The clinician, the pathologist, the research worker, the teacher, and the student have all found a welcome in its pages.

The present issue is intended to be commemorative; it contains a series of brief critical articles by men who have been identified with certain special fields and who have aimed to delineate progress as well as to evaluate the advances which have been made during these past two decades.

The Editors believe that a comprehensive survey of most of the outstanding accomplishments of the period is presented in this anniversary issue. It has not been feasible to include every phase of activity, for the field covered by our specialty has expanded greatly and is no longer limited to the narrower domain characteristic of a half century ago. Gynecology and obstetrics have not only made a closer approach to each other, but they have come to be taught as a unified subject in most of our medical schools and are associated more closely and intimately with the practice of radiology, chemistry, physiology, pathology, and general medicine itself, than was the case in former generations. The increased hospitalization of obstetric patients is likewise a noteworthy development as is the recognition of the need of adequate care for the pregnant woman and of her importance in the social scheme. The strides made in the field of preventive medicine in a larger sense have found likewise their wider application in obstetrics and gynecology. We should be proud to acknowledge the extended participation by American physicians in these advances and their presentation in the pages of the JOURNAL.

To our literary contributors, to our subscribers, to our Advisory Board, to the various societies who have accepted this magazine as their official organ, and to our many friends, the Editors and Publishers of the JOURNAL desire to express their grateful appreciation of the support which has been accorded the venture during these first two decades since its establishment. We trust that we will merit its continuance for many years to come.

*George W. Kosmak
Hugo Ehrenfest
The C. V. Mosby Company*

We are indebted to Dr. Robert L. Dickinson for the specially designed title page in this issue as well as the photographs of the sculptured models of the "Birth Prelude" and the Stages of Labor. The sculptures were done by Mr. A. Belskie.

American Journal of Obstetrics and Gynecology

VOL. 40

OCTOBER, 1940

No. 4

Twentieth Anniversary

1920-1940

TWENTY years ago this month there appeared the first number of a new publication, the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. It was issued in response to a demand for a successor to follow an honored predecessor, the *American Journal of Obstetrics and Diseases of Women and Children*, which suspended publication, by force of circumstances, in December, 1919, after an uninterrupted career dating back to 1868.

A paragraph from the opening announcement of the new JOURNAL may be quoted in this Preface to the present number, which marks the conclusion of a period of twenty years of similar uninterrupted service to the American medical profession in this field.

"The importance of obstetrics and gynecology as an integral part of medical art and science should be measured not only by its interest to those directly engaged in it as a specialty but likewise to those who practice medicine in a more general sense. A topic that necessarily commands the attention of so many physicians must be adequately represented in journal literature and demands a medium of publication primarily devoted to its advancement and welfare. The present venture has been developed in response to this need."

How successful the venture has been may be measured by the growth of the JOURNAL and its reception by the profession. Among such factors is the increase in the number of specialist societies which have selected the JOURNAL as their official organ and the constantly augmented circle of readers, both here and abroad, to whom the publication appeals as the representative magazine in this field of medical practice in the United States. The demands for space in its pages by authors from all parts of the country constitute a flattering tribute, and so great have these been that all papers emanating from foreign sources have had to be declined for several years. The JOURNAL has retained its catholic character, it has been liberal in its acceptance of contribu-

literature. Untrammelled by any commercial restraints, it has made and earned its own way, walked upon its own feet, and again we are proud of it.

From the first, it has been particularly fortunate in its Editorial Staff; for while its high ideals have been steadily maintained, the balance has been evenly held as between the laboratory and clinical aspects of the work. In consequence, it adequately meets the requirements of the specialist, the research worker, and the man or the woman in general practice.

Trusted within and without, it has been accepted as the official organ of all our important Societies, and so has become the sponsor, as it were, of their respective transactions. While its pages encouragingly reflect each and every special line of research, there is always manifest a critical censorship, so essential to the integrity of our professional life; so indispensable to the health, welfare, and reputation of our specialty.

We heartily congratulate the JOURNAL, its editors, its publisher, and its staff, and it needs no prophet to foretell a long and brilliant future for this distinguished exponent of the fourth estate.

WALTER W. CHIPMAN.

Montreal, Quebec.

August 14, 1940.

An Appreciation

THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY celebrates with this issue its twenty years of service to the medical profession, a special service, devoted exclusively, as its name implies, to the complementary activities of this important specialty.

It is a great honor to share, even in the smallest way, in this well-earned celebration, to pay a deserved tribute to the coming-of-age, as it were, of this journalistic achievement.

And first, we are mindful that this JOURNAL represents, and so much the better, a second incarnation, inasmuch as it has fallen heir to a rich inheritance of tradition and experience. It has profited thoroughly thereby, for the strength of the old has been utilized to the full in this later and larger existence.

Its distinguished progenitor, the so-called "Blue Journal," was one of our earliest American publications. Founded in 1868, this *Journal of Obstetrics and Diseases of Women and Children*, published by William Wood and Company of New York, enjoyed a long and influential career until it finally succumbed in 1919, as a result of the financial depression of the Great War. Brooks H. Wells, whom so many of us gratefully remember as its Editor-in-Chief, had died in 1917. Very fortunately for the future and for us all, some eight years before his death, he had chosen as his associate editor, George W. Kosmak of New York, and it was upon the shoulders of his enthusiastic associate that the mantle fell. Dr. Kosmak who was to ring out the old, and then to ring in the new, was editor of the *Journal of Obstetrics* for the last two years of its existence and then, after a year's interregnum, the founder and Editor of the JOURNAL that now he so ably represents.

This, in a few words, is the history of our JOURNAL, the JOURNAL of our specialty, though nothing is revealed therein of the courage, wisdom, and determination that finally gave it this second birth. We believe that it is fitting to recall something of that famous struggle. Those post-war years were indeed saddened years (this sadness, Heaven knows is with us yet), a time inauspicious for the launching of any enterprise, and especially perhaps for the re-creation of any journal. And yet the Fates were with us, and it was finally accomplished.

It is only fair to say that it was really Dr. Kosmak, a Founder in name and in deed, who drove it through. Loyal friends rallied to his support, notably George Gellhorn of St. Louis, and The C. V. Mosby Company undertook its publication; Hugo Ehrenfest became associate and later co-editor, an advisory board of editors was chosen, as well as a thoroughly representative Publication Committee; and so was born this independent, special JOURNAL, twenty years ago.

And very justly we are proud of it. Even in the adolescent years, it has amply justified its existence, has returned in abundant-fold the terms of its stewardship, and fills today no small place in our medical

Endometriosis may be divided into two main groups, direct (internal) and indirect (external). In the first the ectopic mucosa, usually situated in either the uterine or tubal walls, is continuous with the mucosa lining these organs. The ectopic mucosa in the second group has the same histologic structure as that in the preceding one but is not continuous with normally situated Müllerian mucosa. If the mucosa in this group is derived from the latter it must arise from the transplantation to and the growth of bits of this tissue in new situations. This phenomenon may be accomplished in various ways.

Peritoneal endometriosis, one variety of the indirect group, is usually found on the surface of the various organs and structures primarily or accidentally situated in the female pelvis, especially those in the posterior cul-de-sac. These foci are nearly always multiple and their distribution is very similar to that of peritoneal carcinomatosis secondary to cancer cells escaping into the peritoneal cavity from carcinoma of the ovary and of the body of the uterus. The majority of the lesions of peritoneal endometriosis are small and superficial. Sometimes, however, this ectopic mucosa invades, much like carcinoma, the organs or structures beneath it. The early deposits of endometriosis on the surface of the ovary often differ in no way from similar deposits in other situations of the same case. They may remain small and superficial or become invasive and give rise to endometrial cysts of that organ.

Postoperative endometriosis may be either direct or indirect and offers as large and as interesting a field for the study of this subject as experimental endometriosis in the lower animals.

THE IMPLANTATION THEORY

Ovarian and other forms of peritoneal endometriosis arise from the implantation of bits of Müllerian mucosa, of either uterine or tubal origin, which, having been carried with menstrual blood escaping through patent tubes into the peritoneal cavity, have lodged on the surfaces of the various pelvic structures. The ectopic mucosa in these implants, regardless of their size or situation, may become additional foci for the spread of the endometriosis by direct extension and also by the implantation of bits of Müllerian tissue which escape from them during their reaction to menstruation. This latter phenomenon is most spectacular in the ovary where ectopic endometrial cavities may attain a much larger size than elsewhere, forming the well-known endometrial cysts of that organ.

OBSERVATIONS AND INTERPRETATIONS MADE DURING THE FIRST STEP IN THE DEVELOPMENT OF THE IMPLANTATION THEORY

In the year 1921 I reported 23 cases of endometrial cysts of the ovary under the title "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary: Their Importance and Especially Their Relation to Pelvic Adenomas of Endometrial Type ('Adenomyoma' of the Uterus, Recto-vaginal Septum, Sigmoid, etc.)."

THE DEVELOPMENT OF THE IMPLANTATION THEORY FOR THE ORIGIN OF PERITONEAL ENDOMETRIOSIS

JOHN A. SAMPSON, M.D., ALBANY, N. Y.

EIGHTEEN years have elapsed since the essential features of this theory were published. Ever since that time I have continued to be greatly interested in endometriosis of all types, especially the peritoneal type, not only because it occurs more frequently than all others and is clinically the most important, but also because its pathogenesis is so tantalizingly alluring and elusive.

For over ten years I studied peritoneal endometriosis constantly and intensively, and since then intermittently according to the operative findings in individual cases. During the intensive study of this subject the distribution and character of its lesions were carefully noted at operation. Sketches were frequently made at that time. Great attention was paid to small implants. When feasible these were excised. Drawings, many in color, were made of all specimens of endometriosis before they left the operating room floor. All material was fixed intact in formalin. After fixation, I selected the exact portions of the specimens which I wished to study histologically. This tissue was embedded in celloidin, since it causes less unequal tissue shrinkage than paraffin. I supervised the mounting of the embedded tissue and instructed the technician how it should be cut. A small notebook was carried, in which I jotted down "inspirations" before they vanished. Studies of the peritoneal implantation of cancer cells escaping from carcinoma of the ovary and of the body of the uterus and also studies of the spread of these tumors in other ways, were initiated by my desire to investigate more intelligently the spread of benign Müllerian mucosa.

I enjoyed every bit of the study of endometriosis; there were an abundance of fresh material, excellent laboratory facilities, including well-trained technicians, an artist whose illustrations speak for themselves better than any words I might employ, a cooperative and skilled microphotographer and interested associates. My chief contribution was an insatiable curiosity which, stirred by difficulties and opportunities which were constantly arising, perpetuated my interest.

I greatly appreciate the appraisals of my observations and interpretations which have been made by others. However, it is my own critical evaluation of these observations and interpretations which I shall attempt to present in this review.

The term endometriosis was introduced to indicate the presence of ectopic tissue which possesses the histologic structure and function of the uterine mucosa. It also includes the abnormal conditions which may result not only from the invasion of organs and other structures by this tissue, but also from its reaction to menstruation.

structure and in function? Some may assert that dormant endometrial epithelium may be present in the tissues soiled by the contents of the cyst and this is stimulated to further growth. *It seems to me that the condition found in many of these specimens is analogous to the implantation of ovarian papilloma or cancer on the peritoneal surface of the pelvis from the rupture of an ovarian tumor containing these growths."*

A critical evaluation, based on further studies and greater knowledge, of the observations and interpretations recorded in the first paper follows. The validity of all of the observations has been confirmed by subsequent studies. However, some of the interpretations are not entirely correct.

I then believed that these cysts arose either from a metaplasia of the surface epithelium of the ovary or from congenitally misplaced epithelium of endometrial type in that organ. These theories are not as convincing to me, at the present time, as the implantation theory.

The conclusion that menstruation occurs in these cysts and produces hematomas of endometrial type, identical with those found in adenomyoma of the uterus, has been strengthened by further observations.

The assumption that the fusion of an ovary containing one of these cysts with an adjacent structure is always an indication of the sealing of a perforation of the cyst is not correct. From subsequent studies of the development of endometrial cysts of the ovary I have learned that they arise from Müllerian tissue on the surface of that organ (nearly always the lateral or under surface). Frequently there also is endometriosis on the posterior surface of the uterus or broad ligament in contact with the infected surface of the ovary. These surfaces frequently become adherent to each other before the ovarian cyst actually develops. This fusion arises from two sources: first, the irritation of the peritoneum and surface of the ovary by menstrual blood escaping from the endometriosis in these situations, and second, by the frequent continuity of the ectopic mucosa on the surface of the ovary and adjacent structures. The cyst subsequently developing in the ovary may be entirely surrounded by ovarian tissue, but often a portion of its wall is formed by the uterus or parietal peritoneum fused with the ovary in this situation, thus presenting the appearance of a sealed perforation of the cyst.

The inference that endometrial cysts actually rupture and their contents escape into the pelvic cavity has been confirmed by finding this phenomenon at operation. When pressure is made on such a cyst at that time, more of its contents escape through an opening in its wall at or near its fusion with an adjacent structure. If these patients had not been operated upon, the perforation would later have become sealed and the cyst might again rupture at a later menstrual period.

Subsequent studies of the conditions present in patients with evidence of a recent rupture confirm the original interpretation that the material escaping from these cysts may be very irritating to the peritoneum and adhesions may arise from it, both locally about the site of rupture and also in other portions of the pelvis, especially the bottom of the posterior cul-de-sac. Adenomas of endometrial type (endometriosis) were found in a large percentage of the pelvic structures apparently

Since the study of the material obtained from this group of cases furnished not only the first step in the development of the implantation theory but also both the incentive for and the key to its completion, I am republishing the following verbatim excerpts from the conclusions of the original paper.

"At operation the cyst or ovary is found to be adherent, and in freeing it the 'chocolate' contents escape because a previous perforation, which had been sealed by whatever structure the ovary had become adherent to, is reopened or the cyst is torn. Adhesions, due to the irritating action of the material which had previously escaped from the ovary, are always present, and these vary greatly in location, density and extent. They may be found in any of the natural pockets and folds of the pelvis where such material would be apt to lodge, and especially in the cul-de-sac."

"The exact counterpart of the epithelial lining of these ovarian hematomas may be found in the uterine hematomas often occurring in adenomyoma of the uterus and apparently due to the retention of menstrual blood. Tissue of endometrial type is also present in pockets in the periphery of the ovary about the perforation, and the tissue in these pockets may resemble normal endometrium more closely than that lining the hematoma in the same ovary. The histologic study of these hematomas shows that periodic hemorrhage, similar to that of menstruation, occurs. I have come to the conclusion that these ovarian hematomas are of endometrial type just as are the uterine hematomas found in adenomyoma of the uterus."

"The adhesions form equally as interesting a pathologic study as the cysts themselves because adenoma of endometrial type is present in the tissues involved by the adhesions in a large percentage of cases. I have studied histologically the tissues involved by the adhesions outside of the ovary in fourteen of the twenty-three specimens, and adenoma of endometrial type was found in thirteen of these."

"Sometimes, or possibly many times, in the life of these hematomas, material including epithelial tissue and blood (menstrual) may escape into the peritoneal cavity from the hemorrhagic cyst or from the endometrial pockets in the ovary about the site of perforation and lodging in the natural pockets and peritoneal folds of the pelvis, they may cause adhesions. Adenomas of endometrial type often develop between the adherent folds of peritoneum thus resulting. These adenomas may be small and quiescent or they may be invasive. *If invasive they may cause adenomyoma of the uterus by invasion of the uterine wall from without or adenomyoma of the uterosacral ligament, round ligament, rectovaginal septum, rectum, sigmoid, etc., namely, whatever structure or organ is invaded by the adenoma arising from the infective contents of the cyst or ovary lodging on its surface.* The question naturally arises: In what way do the contents of the cyst or ovary cause the development of these adenomas? Is it due to some specific irritant present in the cyst contents which stimulates the peritoneal endothelium, thus causing a metaplasia and the development of endometrial tissue typical both in

dence of endometriosis in either ovary. The histologic structure of portions of the mucosa of the occluded fimbriated ends of the tubes in this case was similar to that of the mucosa in the associated implant on the posterior surface of the uterus. Bearing in mind the manner of the spread of endometriosis from the ovary to the peritoneum, I inferred that this implant might have arisen from tubal epithelium cast off by the menstrual reaction of the tubal mucosa prior to the complete occlusion of the tubes. I believe that this inference is correct.

Material escaping through patent tubes, therefore, was considered as a possible cause of both ovarian and other forms of peritoneal endometriosis. My present reactions in regard to the above observations and interpretations of the same are well expressed in a paper published in 1927. A verbatim excerpt from this paper follows. "One of the outstanding features of patients with peritoneal endometriosis is that the tubes are usually patent. In 293 cases of peritoneal lesions containing endometrium-like tissue encountered during the last five years, both tubes appeared to be patent in 284, a unilateral hematosalpinx in 3 (in 2 of these blood was present in the opposite tube but the tube was patent), bilateral hematosalpinx in 4, and bilateral pyosalpinx in 2. Patent tubes apparently increase the incidence of peritoneal endometriosis and possibly the relatively large number of patients with hematosalpinx (7) may be of some significance. In the 6 cases with occlusion of both tubes, the peritoneal lesions might have been present prior to the closure of the fimbriated ends of the tubes. It would seem that during the menstrual life of women some substance escapes from the tubes into the pelvis which plays an important role in the etiology of pelvic peritoneal endometriosis, including the development of endometrial tissue in the ovaries. This substance may be menstrual blood in some instances and tubal secretion in others. In either case epithelium may be present."

From careful anatomic studies of the relation between the fimbriae of normal tubes and the surfaces of the ovary and other structures in the pelvis, which were made at that time, I inferred that if implants should arise from epithelium escaping from the mucosa of the tube including its fimbriae or from the uterus, they would occur most frequently on the lateral and under surfaces of the ovaries, the lower portions of the posterior surfaces of the uterus and broad ligament and in the bottom of the cul-de-sac. It is in these situations that the early implants of peritoneal endometriosis had been most frequently observed. Similar observations have been made in subsequent studies.

The variations in the type of the epithelium (either uterine or tubal) in peritoneal endometriosis, the occurrence of mucosa in the fimbriae and ampulla of the tube having the structure and function of the endometrium, and the incidence of direct endosalpingosis of endometrial type following salpingectomy and tubal sterilization, all suggest that peritoneal endometriosis could be derived from tubal as well as from uterine mucosa.

The peritoneal endometriosis associated with endometrial cysts of the ovary, which I had studied up to and including 1922, was more

soiled by the contents of these cysts in the first series of cases studied. Subsequent studies have confirmed this observation. At the time the first paper was published I believed that the Müllerian mucosa in the above described situations arose from the implantation, on the surface of the peritoneum, of epithelium cast off by the menstrual reaction of the lining of the ovarian cyst and carried with its contents, escaping into the pelvic cavity. I also believed that a similar phenomenon occurred from the menstrual reaction of endometrial mucosa on the surface of the ovary about the site of the fusion of the cyst with adjacent structures. Strong circumstantial evidence indicates that peritoneal endometriosis arises from ovarian endometriosis in this manner. Proof will be presented showing that it also arises from other sources and that at least in certain instances some peritoneal endometriosis was present in the pelvis prior to the rupture of the ovarian cyst.

The first step in the development of the implantation theory consisted of strong circumstantial evidence, indicating that peritoneal endometriosis could arise from the implantation of epithelium carried with menstrual blood escaping into the peritoneal cavity from foci of endometriosis in the ovary.

A CRITICAL EVALUATION OF THE OBSERVATIONS AND THE INTERPRETATIONS MADE DURING THE SECOND STEP IN THE DEVELOPMENT OF THE IMPLANTATION THEORY

This was reached in 1922, the year following the publication of the first paper. As a result of greater ability in recognizing the lesions of peritoneal endometriosis at operation, 33 cases of this condition associated with endometrial cysts of the ovary were encountered in one year, as compared with 23 similar cases which had been previously collected over a period of more than ten years. During the same period, 15 additional cases were studied in which there was no gross evidence of an endometrial cyst in either ovary. One or both ovaries had been removed in 13 cases. In 9 of these, tubules or glands of Müllerian type were found on either the lateral or under surface of the ovaries. These were interpreted as structures from which endometrial cysts might arise. In 4 cases no evidence of ovarian endometriosis was detected. Subsequent studies have resulted in similar observations and interpretations.

It was noted that the early lesions of endometriosis on the surface of the ovary and peritoneum in some cases not only had the same gross appearance and histologic structure but also appeared to be of the same age. Similar observations have repeatedly been made since then. Therefore a common source for the endometriosis in both situations was sought. Naturally patent tubes were considered as possible avenues through which Müllerian tissue might escape into the peritoneal cavity.

In the 56 cases of endometrial cysts of the ovary which had been studied up to that time the tubes appeared normal and patent in all. In the 15 cases of peritoneal endometriosis without demonstrable endometrial cysts of the ovary, the tubes appeared normal and patent in all but one. In that case bilateral hematosalpinx was present without evi-

SUMMARY

In studying the pathogenesis of ovarian and other forms of peritoneal endometriosis, one must not lose sight of the important role evidently played by patency of the tubes.

At times, during menstruation, blood, carrying bits of Müllerian mucosa, escapes through patent tubes into the peritoneal cavity. This blood may come either from the uterine or from the tubal mucosa. Circumstantial evidence indicates that Müllerian tissue in this blood, under favorable conditions, becomes implanted on any structure upon which it may lodge. These early primary implants occur most frequently in close proximity to the distal ends of the tubes, such as the lateral and under surfaces of the ovary, the lower portions of the posterior surfaces of the uterus and broad ligaments, and the bottom of the cul-de-sac. They may be present only on the ovary or ovaries, only on the peritoneum, or in both situations. Some of these implants remain small and superficial. The Müllerian mucosa in others invades its host much like implantation carcinoma. When it invades other organs or structures than the ovary, a type of endometriosis arises which both grossly and histologically often closely resembles a direct endometriosis of the uterine wall.

The invasion of the ovary by Müllerian mucosa implanted on its surface and the conditions resulting from it are in many ways similar to those arising from the invasion of the other organs and structures by this tissue except for one very striking difference. The ectopic endometrial cavities distended with menstrual blood in endometriosis, in other situations than the ovary, are usually small while those in the ovary frequently attain a large size, forming the well-known endometrial cysts of that organ. Whether small or large these ovarian cysts often rupture and some of their contents escapes into the peritoneal cavity frequently causing adhesions, and, under favorable conditions, the judged peritoneal implantation of bits of the epithelial lining of the cyst which had been cast off by menstruation. In patients with peritoneal endometriosis associated with an endometrial cyst of the ovary, both primary implants from or through the tubes and secondary ones from the cyst may be present.

The study of peritoneal endometriosis also indicates that menstrual blood may not only escape from foci of endometriosis in other situations than the ovary, but adhesions and an additional spread of the endometriosis (secondary implants) may arise from this source. On account of the usual small size of the superficial foci of serosal endometriosis, the results of their participation in menstruation are not as striking as those which take place in the ovarian cysts.

If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive.

extensive and invasive than that occurring without these cysts. For these reasons the ovary was considered an incubator, hotbed, or even at times an intermediary host in the development of implants on the peritoneum, and might even impart greater virulence to the Müllerian epithelium growing in it. The larger cysts were accompanied by greater pelvic adhesions and a more extensive peritoneal endometriosis than that accompanying the smaller cysts. The study of more material has taught me that extensive peritoneal endometriosis occasionally occurs without any demonstrable ovarian endometriosis and large and very adherent endometrial cysts with extensive adhesions in the cul-de-sac are encountered in which very little endometriosis is found in the organs and other pelvic structures involved by these adhesions. Therefore the suggestion that the ovary may impart greater virulence to the Müllerian epithelium growing on it is unwarranted.

It is true that there is *no positive proof* that epithelium escaping from these cysts becomes implanted on the peritoneum. However, a careful study at operation of the conditions present in a large number of cases of endometrial cysts will convince even the most skeptical observer that the material escaping from these cysts frequently causes adhesions, and the evidence indicating that the Müllerian mucosa in these situations at times comes from the contents of the cyst is very strong.

Because I believed in 1922 (and still believe) that implantations on the peritoneum arise from epithelium carried by menstrual blood escaping from ovarian endometriosis both from the cysts and the non-encapsulated endometrium on the surface of the ovary and also from endometrial foci in the tubal mucosa, I suggested that menstruation with a backflow through the tubes may play an important role in the etiology of ovarian and other forms of peritoneal endometriosis. At that time I did not know whether or not this phenomenon occurred.

Since 1922 many patients, requiring pelvic operations, have purposely been operated upon during menstruation. Not infrequently blood was observed escaping through the patent abdominal ostia of the tubes of these patients. This occurs in patients with and without peritoneal endometriosis. Bits of viable appearing uterine mucosa surrounded by blood were found in sections of some of the above described tubes after they had been fixed in formalin.

The detection of peritoneal endometriosis with and without ovarian involvement led to the second step in the development of the implantation theory. This consisted of strong circumstantial evidence indicating that bits of Müllerian tissue, derived from both the uterine and the tubal mucosa and carried by menstrual blood escaping through patent tubes into the peritoneal cavity, could become implanted on various pelvic structures including the ovaries, and the resulting perforating hemorrhagic ovarian cysts are only spectacular foci in the secondary spread of endometriosis.

Subsequent studies have shown that a secondary spread of endometriosis also could arise from foci in other situations than the ovary. This latter phenomenon constituted the third and final step in the development of the implantation theory.

THE MORE RECENT CONCEPTIONS OF THE PELVIC ARCHITECTURE

W. E. CALDWELL, M.D., F.A.C.S., H. C. MOLOY, M.D., M.Sc., AND
D. ANTHONY D'ESORO, M.D., New York, N. Y.

RECENT anatomic and roentgenologic studies have shown, to the satisfaction of most observers, that variations in the size and shape of the pelvis occur more frequently than was hitherto suspected. Certain characteristic types have been described in detail and more recent studies have gone far toward appraising the significance of these variations upon the mechanism of labor. The chief differences in opinion among interested workers, at the present time, concern the correct classification of these variations. The material that follows will be limited to the more important observations we have made during the last eight years in a study directed toward the description and classification of these variations.

CLASSIFICATION OF PELVES

In studying the classifications proposed by such authorities as Michaelis, Litzmann, Tarnier, Budin, Schauta, Breus and Kolisko, and others, some wholeheartedly accepted the principle that an obstetric classification should be arranged according to the etiology of the factors which caused the distortion. They attempted to fit abnormalities of doubtful origin into appropriate sub-groups. Others, recognizing the prevalence of pelvic abnormalities for which no known explanation existed, introduced such morphologic terms as "flat nonrachitic pelvis," "funnel pelvis," or "generally contracted type." Although Michaelis and Litzmann favored the morphologic school of thought, the preconceived methods of etiologic grouping and lack of concrete knowledge prevented the general acceptance of their views. Anatomists and anthropologists have always considered form in the study of unknown skeletal material. Stein (1825) distinguished four groups: (1) Elliptical with the greatest diameter anteroposterior, (2) round, (3) elliptical with the greatest diameter transverse, (4) blunt-heart shaped. Turner in 1885 proposed a morphologic classification based upon the relationship between the transverse and anteroposterior diameter of the inlet. He divided pelves into three groups: (1) Dolichopellie, in which the conjugate vera is greater than the transverse, (2) mesatipellie, in which the conjugate vera and transverse diameter are of equal length, (3) platypellie, in which the conjugate vera is shorter than the transverse diameter. Thoms has recently revised Turner's classification and has added a fourth group, the brachypellie form. During the early part of this century, anthropologists made a number of significant observations which have not been fully appreciated. Wood Jones and Elliot Smith, during excavation in Nubia in 1906, observed numerous examples of extreme masculine types of female pelves. Derry, Straus,

The viability of this theory is of secondary importance to me as compared with the pleasure and the increased knowledge of this and kindred subjects which I have gained in these studies and the resulting more intelligent treatment of patients who have peritoneal endometriosis. There are many other interesting unsolved problems associated with the pathogenesis and life history of endometriosis of all types. Since it is my desire to adhere strictly to the text which has been assigned me, I have not discussed any of these.

REFERENCES

- (1) Arch. Surg. 3: 245, 1921. (2) Boston M. & S. J. 186: 445, 1922. (3) AM. J. OBST. & GYNEC. 4: 451, 1922. (4) Arch. Surg. 5: 217, 1922. (5) Surg. Gynec. Obst. 38: 287, 1924. (6) Arch. Surg. 10: 1, 1925. (7) AM. J. OBST. & GYNEC. 10: 462, 1925. (8) Ibid. 10: 649, 1925. (9) Ibid. 12: 459, 1926. (10) Ibid. 14: 422, 1927. (11) Am. J. Path. 3: 93, 1927. (12) AM. J. OBST. & GYNEC. 16: 461, 1928. (13) Ibid. 18: 1, 1929. (14) Ibid. 20: 443, 1930. (15) Ibid. 24: 497, 1932.

3. *The Platypelloid Type* (Greek, *Platys*, flat, + *pellis*, pelvis). The anterior and posterior segments combine to give a transverse oval or flat form. The side walls are straight and the subpubic arch is wide.

4. *The Android Type* (Greek, *Aner*, man). This type bears a resemblance to the male pelvis at the inlet and at lower levels. The posterior segment is flat and the widest transverse diameter is close to the sacrum. The anterior segment is triangular in shape. The two segments combine to produce a wedge-shaped appearance. At lower levels, the side walls show convergence, the subpubic arch is narrow, and the sacrum is forward.

Each pure type shows a characteristic shape for both segments at the inlet and also at the mid and lower pelvis. Pure types occur less frequently than "mixed" forms which reveal a departure from the characteristic shape of the parent type either at the inlet, in the pelvic cavity, or in both. Certain pure types with characteristic inlet shapes may show variations below the inlet. These forms are classified according to the inlet shape, augmented by descriptive terms which describe the lower pelvic deviations. For instance, pelvises which reveal anthropoid or gynecoid inlet types become "mixed forms" through the presence of convergence of the side walls, a narrow subpubic arch, a forward lower sacrum, or some other departure from the classic anthropoid or gynecoid pure type. Android types may become "mixed forms" by revealing straight side walls, or a wide subpubic arch, or any other departure from the classic android shape in the mid or lower pelvis.

In other mixed types, the inlet differs from the pure forms in addition to the presence of lower pelvic variations. These forms require a modified terminology to define the inlet shape before the lower pelvis is described. In these examples the posterior segment may conform to the shape of one parent type and the anterior segment to that of another. In the classification of these mixed types, the first term indicates the shape of the posterior segment, and the second term the shape of the anterior segment. Theoretically at least, the posterior segment of any one of the four parent types may be combined with the anterior segment of the other three to give three mixed forms. For example, the gynecoid posterior pelvis, when associated with the anterior segment of an anthropoid, android, or flat parent type, results in "gynecoid-anthropoid," "gynecoid-android," and "gynecoid-flat" types.

The anthropoid posterior segment combines commonly with only two parent anterior segments, the gynecoid and android, to form "anthropoid-gynecoid" and "anthropoid-android" types. Theoretically at least, an "anthropoid-android" type could occur to designate anthropoid types with a narrow fore pelvis, but these forms are usually considered as pure anthropoid types. At the present time, our knowledge of these variations is too incomplete to assume that a narrow fore pelvis necessarily represents a masculine characteristic in all instances. For example, the term "gynecoid-android type," described above as a gynecoid mixed type, actually refers to a "gynecoid pelvis with a narrow fore pelvis." We have encountered a few examples in which the shape of this narrow fore pelvis appears to resemble a masculine characteristic, but in others, the narrow fore pelvis does not present a

and others, have described in detail the masculine characteristics which may aid in the determination of the sex of unknown skeletal material. Recent anthropologists such as Hrdlička, Todd, Hooton, Schultze, Shapiro, and others, are convinced that the variations in pelves are too complex to be grouped in the simplified classifications proposed by Weber, Stein, and Turner. Shapiro, at the American Museum of Natural History, has summarized anthropologic opinion by considering these diversified forms as *normal growth variants*.

This brief review of the literature gives the requirements which must be fulfilled by any comprehensive classification. A classification of pelves which will prove of maximum clinical value and lead to a better understanding of the mechanism of labor is based, necessarily, on morphology. It should be comprehensive enough to permit the classification of rare forms as well as the common types. It should provide an accurate description of the pelvic canal as well as the inlet and outlet. A suitable terminology, with appropriate descriptive terms, must be devised to enable obstetricians to give a reasonably accurate concept of the size and shape of the pelvis as a whole. We have attempted to fulfill these requirements in the classification described in this report.

Eight years ago at the Sloane Hospital for Women a group became interested in the causes of dystocia. In a short time, from the study of skeletal pelves at the American Museum of Natural History, New York; the United States National Museum, Washington; and especially Todd's large collection of pelves of known sex at Western Reserve University, Cleveland; and by roentgenologic examinations upon living women, we recognized the types described by Stein and Turner and the masculine form long known to anthropologists. The reports of Wood Jones, Berry Hart, Derry, Straus, and others, were most helpful in the analysis of these variations. We found that division of the inlet into an anterior and posterior segment at the widest transverse diameter aids in the analysis of pelvic shape. The posterior segment behind the widest transverse diameter is formed by the sacrum and a portion of the two iliac bones above the sacrosciatic notch. The anterior segment in front of the widest transverse diameter is formed by a small portion of both iliac bones and the superior rami of the pubis along the iliopectineal lines.

The study of this material resulted in the recognition of four parent, or pure, types to form the basis for a morphologic classification of pelves. The following terms were proposed to describe the parent types:

PARENT TYPES

1. *The Anthropoid Type* (Greek, Anthrōpos, human being + Eidos, resemblance). This pelvis resembles the shape of the pelvis of the anthropoid apes. The anterior and posterior segments together present a long narrow oval shape. The side walls are straight, the subpubic arch is under average in size, and in the classic type, the sacrum shows an average inclination.

2. *The Gynecoid Type* (Greek, Gynē, woman). This is the so-called normal female pelvis. The anterior and posterior segments give a round or transverse slightly ovoid shape. The side walls are straight, the subpubic arch is wide, and the sacrum shows an average to backward inclination.

Dr. Kyle B. Steele, at the New York Lying-In Hospital, during the last few years, has made extensive use of our original work sheet. He has recognized the fourteen inlet types and has devised standard shapes (in cardboard) for the anterior and posterior segments of the four parent forms. These inlet tracings may be fitted into the image in the precision stereoscope to aid in the diagnosis of unusual mixed forms. They are excellent for teaching purposes. In his opinion, the principle of combining anterior and posterior segments represents a comprehensive and practical method for the recognition of the pure and mixed forms. Other workers, among them Rappaport and Seadron; Pettit and associates, and Walsh, have reported similar observations.

We have studied, up to the present time, over 3,000 roentgenologic case studies; in not more than an estimated 2 per cent has a recognized cause for the pelvic abnormality been found. Rickets accounts for about half of these, or 1 per cent of all pelves studied, and the other half is accounted for by a variety of causes. Many of these distinctly pathologic types may retain their primary shape to such a degree that the pelvis may be classified upon a morphologic basis similar to the classification of the normal growth types. The degree of the pathologic distortion can be described in general terms. If approximately 98 per cent of all pelves are considered normal growth variants, it follows that the classification of these forms must be placed on a morphologic basis and given prominence in all formal classifications.

Hitherto, we have made no attempt to combine these morphologic forms with the infrequent pathologic types in a classification. Recently this was done through the interest of Dr. Henricus Stander. All the rare forms described in the last edition of Williams' textbook have been included. The complete classification as approved by Dr. Stander is arranged as follows:

MORPHOLOGIC TYPES

I. *Normal Female Growth Types:*

(Each inlet type must be augmented with appropriate terms to describe the lower pelvis chosen from list of terms given in Group II.)

- | | |
|-----------------------------|---|
| 1. True anthropoid type | Transversely contracted type |
| 2. Anthropoid-gynecoid type | |
| 3. Anthropoid-android type | Anthropoid with narrow fore pelvis |
| 4. True gynecoid type | Normal female pelvis |
| 5. Gynecoid-anthropoid type | |
| 6. Gynecoid-android type | Gynecoid with narrow fore pelvis |
| 7. Gynecoid-flat type | |
| 8. True android type | Masculine type, funnel type |
| 9. Android-anthropoid type | |
| 10. Android-gynecoid type | |
| 11. Android-flat type | |
| 12. True platypelloid type | |
| 13. Flat-gynecoid type | Difficult to distinguish from gynecoid-flat |
| 14. Flat-android type | Difficult to distinguish from android-flat |

II. *Terms Used in Describing the Morphology of the Mid and Lower Pelvis to Augment the Inlet Classification:*

- | | |
|--|-----------------------|
| 1. Pelvic size | Large, average, small |
| 2. Pelvimetry measurements of cardinal diameters | |

masculine appearance. It may resemble the type of narrow fore pelvis commonly found in anthropoid forms.

The combination of an anthropoid posterior pelvis with a flat anterior segment is, of course, impossible.

The android posterior segment is frequently found associated with a gynecoid, anthropoid, or flat anterior segment to produce "android-gynecoid," "android-anthropoid," and "android-flat" forms. We have suggested that the term "android," when used as the second term in mixed forms, indicates a narrow fore pelvis. "Android-anthropoid" types likewise possess a narrow fore pelvis. The anthropoid character, indicated by the second term, is caused by the long anterior sagittal diameter. The posterior segment of flat types likewise may be associated with gynecoid or android anterior segments to produce "flat-gynecoid" and "flat-android" mixed types. These mixed flat types are difficult to distinguish from "gynecoid-flat" and "android-flat" forms. Although we have included "flat-gynecoid" and "flat-android" types in the formal classification, in actual practice, mixed flat forms are classified usually as the "gynecoid-flat" or "android-flat" variety.

Following the classification of the inlet shape, the variations in the mid and lower pelvis must be considered before a comprehensive classification has been obtained. In spite of a desire for simplicity, the occurrence of lower pelvic deviations necessitates the use of further descriptive terms. Fortunately, for many years, obstetricians have used terms such as "wide" or "narrow" subpubic arch, "prominent ischial spines," or a "forward lower sacrum." For practical purposes, we have found that the list of terms, given elsewhere in this report, adequately describe the pelvis below the inlet, in the classification of routine case studies (see classification Group II). The comprehensive description and classification of variations in the pelvis, as outlined above, was incorporated into a work sheet which we used in charting the frequency of occurrence of the various types. This work sheet, as originally devised, included fourteen parent and mixed types along with appropriate descriptive terms for the mid and lower pelvis (see complete classification).

In reporting the observations gained from the use of this work sheet in the study of routine cases, we departed from the original fourteen types. We did not include the "anthropoid-android" and the "gynecoid-android" types, because we failed to apply rigidly the principle that the term "android," when used as the second term in a mixed type, indicates a narrow fore pelvis. As a result, the gynecoid-android type was classified as a "gynecoid or normal pelvis with a narrow fore pelvis." Many anthropoid types with a narrow fore pelvis were classified as pure types. A few of these forms are, however, more correctly considered as "anthropoid-android" types. In the original article we described three flat forms: the "gynecoid-flat," the "android-flat," and the "true flat" or platypelloid type. If, however, careful attention is directed to the study of the shape of the anterior and posterior segments in flat forms, "flat-gynecoid" and "flat-android" types may occasionally be found.

VI. *Types Secondary to Abnormalities of the Lower Extremities:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Luxation of femora
2. Atrophy or loss of one or both extremities

In the study of routine cases, "mixed" types may occur which afford great difficulty in their correct grouping within this morphologic classification. A certain pelvis, to one observer, may conform to the "gynecoid-anthropoid" type, while to another it may resemble the "anthropoid-gynecoid" form. Hrdlička has intimated that many pelves may be encountered which are difficult to classify, inasmuch as one normal growth type blends imperceptibly with another. Pelves which tend to favor one or more of the mixed types usually possess compensatory space due to the well-formed anterior or posterior segment. This latter point should be emphasized in the description of these unusual mixed forms rather than the precise inlet classification. In most instances the pelvic inlet is symmetrical but minor examples of asymmetry may occur. A few of these asymmetrical types may show masculine characteristics on one side, while the other displays the usual female contours.

Since a simple morphologic classification of a few standard types is totally inadequate, the obstetrician must finally accept the fact that the best classification is one which enables him to appreciate the obstetric capacity of the pelvis, and to use descriptive terms which convey a reasonably accurate concept of the pelvis as a whole. From the standpoint of roentgenologic technique, these variations in pelvic morphology cannot be studied with accuracy by single flat anteroposterior films. Stereoroentgenograms viewed in the precision stereoscope which corrects distortion should form the basis for the roentgenologic technique if accuracy in the classification of the pelvis is desired.

CLINICAL RECOGNITION OF THE ABNORMAL PELVIS

Pelves with ample diameters and a wide subpubic arch may be classified as gynecoid types. On x-ray examination, these cases may prove to be ample anthropoid types, or even large android forms. When the promontory can be reached, the diagnosis of a flat type is made, if the pelvis seems wide at the interspinous diameter. If, however, the ischial spines are prominent, the sacrospinous ligament is short, the sacrum is forward, and the subpubic arch is narrow, the diagnosis of a true android type may be made. The small gynecoid type may be difficult to recognize, because it suggests one of the more abnormal forms. But this is not a serious clinical error, since a small gynecoid type may give rise to as much dystocia as other abnormal forms.

Extreme anthropoid types are quite easily recognized clinically. The diagonal conjugate is long, and the promontory cannot be reached, except in the small types. The diagnosis is dependent upon the recognition of a decrease in transverse space throughout the pelvis, not only at the interspinous level, but in the regions above the ischial spines. In

3. Posterior segment of inlet	Gynecoid, android, anthropoid, flat
4. Anterior segment of inlet	Wide, average, narrow
5. Symmetry of inlet	Symmetrical, asymmetry to right, asymmetry to left
6. Pelvic bones	Heavy, average, light
7. Retropubic angle	Wide, moderate, narrow
8. Subpubic arch	Wide, moderate, narrow
9. Pubic rami	Straight (Gothic arch) or curved (Norman arch)
10. Pubic symphysis	Masculine or feminine type
11. Side walls of pelvis	Divergent, straight, or convergent
12. Ischial spines	Long, sharp, or flat
13. Apex of sacrosciatic notch	Wide, average, narrow
14. Base of sacrosciatic notch	Wide, average, narrow
15. Sacrum	A general concept of length, width, number of segments
16. Sacral curvature	Straight, average, marked
17. Sacral inclination	(a) upper portion—forward, average, backward (b) lower portion—forward, average, backward
18. Shape of terminal sacrum	Blunt, average, sharp
19. Lateral bore	Straight, convergent, divergent

PATHOLOGIC TYPES

III. *Abnormal Growth and Developmental Types:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Infantile
2. Dwarf

IV. *Types Caused by Disease of the Pelvic Bones and Joints:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

A. Metabolic:

1. Rachitic:
 - a. Flat
 - b. Generally contracted and flat
 - c. Generally contracted
2. Osteomalacic

B. Congenital, infectious, and atypical types:

1. Assimilation pelvis
2. Split pelvis
3. Naegele's pelvis
4. Robert's pelvis
5. Coxalgic
6. Coxarthrolithetic
7. Pelvis spinosa
8. Neoplastic

C. Traumatic types:

1. Fracture of pelvis
2. Separation of symphysis

V. *Types Secondary to Abnormalities in the Spinal Column:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Kyphotic pelvis
2. Kyphorachitic pelvis
3. Scoliotic pelvis
4. Kyphoscoliotic pelvis
5. Kyphoscoliorachitic pelvis
6. Spondylolithetic pelvis

CHANGING CONCEPTIONS OF OVARIAN TUMORS

HOWARD C. TAYLOR, JR., M.D., NEW YORK, N. Y.

THE last twenty years have witnessed unexpected progress in the study of the nature and behavior of ovarian tumors. The greatest advances have, surprisingly enough, been made in those aspects which had previously been regarded as more or less complete, namely in the basic problems of morphology and classification. Clinical advances for the most part have occurred secondarily as the result of a better differentiation of the individual types of ovarian new growth and in a clearer grasp of the special manifestations of each.

In 1920 the most commonly accepted classification of ovarian tumors differed little from that of Pfannenstiel,⁴⁰ published before the turn of the century. Yet observations were already in the literature which would later force a reclassification, and in 1920 there were signs that a change was imminent. Norris³⁰ in the first volume of this JOURNAL described an "ovary containing endometrium" and recalled a similar case reported by Russell⁴⁵ in 1899. At this time Sampson's⁴⁶ first paper, showing the extraordinary frequency of the endometrial new growths of the ovary, must already have been in preparation. As an introduction to another group of neoplasms, von Kahliden¹⁴ in 1895 had reported what appears to have been a granulosa-cell tumor under the title "graaian follicle adenoma" and twenty years later Meyer²³ had described both the cylindromatous and folliculoid types. American gynecologists were, however, to remain completely unaware of these new growths for some years thereafter and to continue to refer vaguely to the "solid tumors of the ovary." The Brenner tumors, which had probably first been noted by Orthmann³⁹ in 1899 and described anew but erroneously classed as "oophoroma folliculare" by Brenner³ in 1908, were to wait still longer until 1932 for their status to be clarified (Meyer²⁷). Pick⁴¹ had reported the testicular adenoma in 1905, but again many years were to pass before any special attention was to be accorded the arrhenoblastoma (Meyer²⁵). Dysgerminomas, finally, were in 1920 a confused group, lost under a variety of titles. Instead of these tumors, more or less familiar to present-day gynecologists, there flourished a variety of now apparently extinct forms, large-cell carcinomas, endotheliomas, embryonal carcinomas, round cell sarcomas, peritheliomas, and a list of growths supposed to be of teratoid origin.

REORGANIZATION OF THE PATHOLOGY OF OVARIAN TUMORS

The work of the last twenty years, headed by a few outstanding contributions, has been participated in by pathologists and gynecologists throughout the world. These by their combined efforts have sorted out the newly recognized varieties of ovarian tumor and are now gradually accumulating the material to show their frequency, special clinical char-

anthropoid types, the sacrospinous ligament is long if the sacrum has an average inclination. The narrow retropubic angle can also be palpated.

In the typical android type, the sacrosciatic notch is narrow, the sacrum has a forward inclination, and the sacrospinous ligament is short. It is important to distinguish between the adequate pelvis with a forward lower sacrum and android types in which a forward sacrum represents only one of the many masculine characteristics present.

Occasionally the recognition of a narrow subpubic arch leads to the diagnosis of an android or anthropoid type. Although a narrow subpubic arch is more commonly associated with these primary types, certain gynecoid forms may also demonstrate this abnormality in the lower pelvis. We advise an x-ray examination for all cases clinically suspected of possessing one or more abnormalities. Study of the stereoroentgenograms either confirms the obstetrician's clinical impression or indicates the source of his error.

ROENTGENOLOGIC RECOGNITION

Certain roentgen methods of pelvimetry have been simplified to consist of not more than two films, a lateral and an anteroposterior view. While these views are adequate for the purpose of roentgen measurement, they are not satisfactory for a comprehensive study of pelvic morphology.

Our interest in the morphology of the pelvis in living women led Dr. Golden and Dr. Swenson, of the Roentgen-Ray Department of Presbyterian Hospital, to suggest the use of stereoroentgenograms. This method has been found entirely satisfactory for visualization of the pelvis and the fetal pelvic relationship. The technique includes stereoroentgenograms, a lateral view and a forty-five-degree angle view of the subpubic arch. One of us (H. C. M.) has developed a stereoscope which allows the observer to measure the phantom image, and to obtain dimensions of the cardinal pelvic diameters.

While exact diameters may be attained by roentgen methods, in actual practice the significance of these measurements is difficult to determine. One of the serious drawbacks to the use of a few cardinal diameters as a basis for prognosis is the fact that compensatory space does not enter into such calculations. We are opposed to the use of roentgen methods of prognosis which are based on the results obtained from mathematical formulations of a few pelvic and fetal diameters. The ultimate outcome of labor depends upon many other factors. The intricate variations in pelvic shape, although theoretically expressible in centimeters, cannot be so designated in practice; they can only be observed and expressed in descriptive terminology.

Kleine¹⁷) suggest its close relationship. Its rare and relatively slight clinical significance seems to forbid an independent position in any classification. Some anglicized version of the name suggested by Plaut,⁴³ "fibroepithelioma mucinosum benignum," would appear a logical designation. The Brenner tumor probably bears the same relationship to the pseudomucinous cystadenoma as that of another solid tumor, the rare "fibroma adenocysticum serosum" (Frankl⁹; Neumann²⁹) to the serous cystadenoma. A vast simplification would follow the adoption of the terms, pseudomucinous fibroadenoma (Brenner) and serous fibroadenoma (Frankl).

The Brenner tumor, although first reported in Germany, has been much studied in this country. Among the earliest reports were two cases published in this JOURNAL in 1934 (Wolfe and Kaminester⁵⁷; Maury and Schmeisser²⁰). The present knowledge of this tumor has been well summed up by Novak and Jones³⁷ who noted that up to 1938 one hundred and twenty-two cases had been reported in the literature. These tumors are almost invariably benign and exert no endocrine influence. The principal problem they present is the confusion that they may cause the uninformed who often mistake them for granulosa cell tumors, endotheliomas or even Krukenberg tumors.

B. The Connective Tissue Tumors: The benign fibroma of the ovary has, in general, maintained its classic position among ovarian tumors, although a few of the growths formerly placed in this division have recently had their classification altered to that of theca cell tumor.

The once not unusual sarcoma of the ovary has on the other hand all but disappeared. One group, until recently called large round cell sarcoma, has been re-examined and its members distributed among the granulosa cell tumors and the dysgerminomas, while more and more of the so-called fibrosarcomas have been conceded to be benign and regarded as simply cellular fibromas. Caylor and Masson⁴ noted four instances of fibrosarcoma arising among 280 specimens of fibroma, and even of these none had developed metastasis or recurrence when their paper was published. For contrast it is interesting to note that Scheffey⁴⁷ in 1925 had found reports which indicated that sarcoma represented about 4 per cent of all ovarian tumors. The question now may be asked whether there has ever been a sarcoma of the ovary unless the granulosa cell tumor be accepted as arising from the stroma cells and therefore essentially a malignant connective tissue tumor.

C. Teratomas: The status of the common cystic teratoma or dermoid has not changed in the last twenty years, and few determined efforts have been made to solve the perplexing problem of its origin. Reports have continued to indicate that not too infrequently dermoids may give rise to squamous cancer (Counsellor and Wellbrock⁶). A type of teratoma, the struma ovarii, has received some special attention and the functional behavior of its thyroid tissue studied (Plaut⁴⁴). Malignant teratomas have been occasionally reported, but it now appears that they too have lost some of their representatives to other classifications.

D. Specific Tumors of the Ovary: For several years it has been common practice to associate three ovarian tumors together, namely the

acteristics and particularly their relative malignancy. To evaluate this work, it is necessary to consider the progress made with each type of neoplasm.

I. *Cysts of the Follicle and Corpus Luteum*.—That the simple cysts based on persistent follicles or corpora lutea were not true tumors has long been recognized. Newer conceptions have served to emphasize this distinction and to place the cystic Graafian follicle or corpus luteum among the signs of disturbed ovarian function and to remove them more definitely from the list of ovarian neoplasms. Their fuller understanding has become a problem for the endocrinologist.

II. *Endometrial (Chocolate) Cysts*.—The years since the publication of Sampson's⁴⁶ paper have been much occupied with controversy as to the source of the abnormally placed tissue. Its origin has been claimed to lie in viable fragments of uterine mucosa, passing through the tubes at the time of menstruation (Sampson⁴⁶); in particles transplanted by way of the lymphatics (Halban¹³; Mestitz²²); in a metaplasia of the serosa at the site of the new growth (Meyer²⁴; Lauche¹⁸; Novak³²), and in the epithelium of degenerating follicles or corpora lutea (King¹⁵). The controversy, though undecided, has added a store of incidental information about the disease which has aided in establishing the clinical picture and formulating a general plan of reasonable therapy. Nevertheless, since the origin of the disease is not agreed upon and may even lie outside of the ovary itself, the endometrial cysts must be given a special position as distinct from all of the definitely primary ovarian tumors.

III. *The Primary Tumors of the Ovary*.—Views now generally held apparently require that there continue to be three groups of primary ovarian tumors that have been accepted, and a fourth whose discovery is essentially the work of the last twenty years. To these may perhaps be added for convenience a fifth group to include miscellaneous or rare tumors whose very existence is somewhat in doubt.

A. *The Epithelial Tumors*: These must be divided, of course, into two distinct types, the one based on a "serous," the other on a "pseudomucinous" epithelium. These two have been recognized for many years and little has recently been accomplished towards determining their cause or the source of the cells composing them.

In one respect, however, some advance has been made with these, namely in the better evaluation of the histologic criteria of their malignancy. Twenty years ago many reports betrayed an unprecise use of the term "cystadenoma," for a percentage of such tumors were evidently regarded as malignant and caused recurrences, as did the papillary cystadenocarcinomas. Although the terms are now used more consistently, the extraordinary difference in the rate of cures still reported for cancer of the ovary by different observers strongly suggests that successful statistics are the result of the inclusion in a given series of at least a certain number of essentially benign tumors.

The Brenner tumor, a newly recognized form, is perhaps best classifiable with this group. The presence in the tumor of mucous glands and its not infrequent concurrence with a pseudomucinous cyst (Abraham¹;

the celomic endothelium, from the granulosa cells of the follicle, or from embryonal rests of these cells ("granulosaballen"). The extraordinary work of Furth and Butterworth¹⁰ on the production of granulosa cell tumors by the irradiation of the ovaries of mice contains evidence that these tumors may arise on the basis of regenerative processes in the remnants of follicular epithelium or in the interfollicular spindle-shaped cells themselves. This origin from the ovarian mesenchyme has also been favored by Traut and Butterworth.⁵⁴ Such a view is rather shattering to the conventional theory of origin of the active cells of the ovary from the germinal endothelium but is supported by Fischel's⁷ evidence for the origin of the follicular epithelium from the ovarian mesenchyme.

2. *The arrhenoblastoma* has made itself known on account of the bizarre masculine changes which take place in the female constitution when such a tumor is growing. The tumor is of course not of great practical importance, for Novak³³ could find but 45 reported cases in the literature up to 1938. Its scientific importance lies in the information it contributes to the origin of certain of the secondary sex characteristics. This whole relationship has, however, remained greatly confused by the appearance of signs of virilism with what appear to be hypernephromas of the ovary (Novak³³), as well as in cases of apparently typical granulosa cell tumors (Bergstrand²).

3. *The dysgerminoma*, the third of the three special tumors, is of interest because of its morphologic identity with a tumor of the testis and because of its tendency to occur in pseudohermaphrodites. This tumor also is probably more frequent than was once supposed. Klaften¹⁶ notes that dysgerminomas represented 3.1 per cent, and Födel⁸ 4 per cent of all malignant ovarian tumors.

The question of the malignancy of this tumor is likewise still being studied. Seegar⁵³ has reviewed 98 cases and found that about 50 per cent of the patients have remained well for five years. Födel,⁸ however, noted that among 55 cases reported in the literature and followed over an adequate period of time, 68 per cent had developed metastases. These figures certainly establish the malignancy of most of these tumors, and it seems questionable whether benign forms of dysgerminoma exist.

E. Tumors of Doubtful Status: Besides the list of currently acceptable ovarian tumors, there have always been a few others. These are either somewhat discredited forms still prized by the more traditional pathologist or newcomers, candidates vigorously supported by their discoverers. Most of them are sufficiently rare to make it necessary for judgment on them to be long delayed. Of the first group may be mentioned the endothelioma or perithelioma which is perhaps on its way to the discard. Of the second group is the mesonephroma, described recently by Schiller⁵⁰ but still waiting to attain recognition. Finally there is the hypernephroma which for years has contended with the luteoma for a position among the ovarian tumors (Schiller⁴⁹; Glynn¹²; Novak³³; Novak and Wallis³⁸).

granulosa cell tumor, the arrhenoblastoma, and the dysgerminoma. There is some justification for this grouping, since the origin of each, according to current theory (Meyer²⁶), is to be found in the specific gonadal cells and with each there is a relationship to the hormones of the gonad or to the development of the secondary sex characteristics. These qualities and the symptoms dependent upon them are too familiar for repetition here, but certain points in the development of the knowledge of these tumors deserve comment.

1. *The granulosa cell tumors.* The apparent importance of the granulosa cell tumors has steadily increased, as their frequency has become more evident. On account of its suggestive structure the folliculoid type was the first to attract attention, but recognition of various less definite forms having a cylindromatous, acinar, or even diffuse structure soon followed. To this basic group must now, tentatively at least, be assigned two somewhat more distinct forms, the "luteinized" granulosa cell tumor or "folliculoma lipidique" of Lècène (Moulonguet²⁸) and the theca cell tumor. Some controversy exists over the possible identity of the "luteoma" and the "hypernephroma" of the ovary, although examples of granulosa cell tumors with isolated areas of luteinization appear to establish the occurrence of at least the partially luteinized form (Plate⁴²; Traut and Butterworth⁵⁴; Traut, Kuder and Cadden⁵⁵). The existence of the theca cell tumor also can scarcely be questioned (Löffler and Priesel¹⁹; Melnick and Kanter²¹), but a disagreement exists as to whether it should be placed in the granulosa cell group or given an independent status. A difference in age incidence, in cellular morphology, and in lipid distribution suggests that they be segregated as a special type (Geist¹¹) but their probable common origin from ovarian mesenchyme, their common property of hormone production and the occurrence of an occasional tumor combining both theca and granulosa cell elements seem to permit their classification as a subdivision of the granulosa cell group.

As a result of these accretions the granulosa cell tumors have become not infrequent. By 1936 Novak and Brawner³⁴ were reporting that 14 per cent of a series of 300 malignant ovarian neoplasms were of this type. Klatfen¹⁶ noted a frequency of 10.1 per cent of 188, and Förderl⁸ 18 per cent of 319 primary ovarian cancers.

The degree of malignancy of the granulosa cell tumors has not been finally settled. In general they are probably less liable to lead to a fatal recurrence than are the common papillary cystadenocarcinomas. However, to call a tumor benign simply because there is no recurrence after its removal is a fallacious line of thought, though it appears to have been followed by some writers. Varangot,⁵⁶ after reviewing reports of 261 cases of granulosa cell tumor, noted that in 10 per cent metastases were already present at the time of the operation and that, particularly if the patients were followed for a long period of time, late recurrences were common. The histologic criteria of malignancy in these cases are badly in need of study.

The origin of the granulosa cell tumors also has been a matter for dispute. The older theories derived them from various sources, from

changed little in the last two decades. In particular in only a few respects have advances been made which were not incidental to the basic changes in pathologic conceptions just outlined.

Symptomatology.—The chief contribution to the symptomatology of ovarian tumors has been made in respect to the special tumors and the changes in the secondary sex characteristics dependent upon the hormones produced by them. Besides this really important advance, there may be mentioned only a commoner recognition of the acute symptoms associated with a ruptured follicle cyst and perhaps a better understanding of the effects of ovarian tumors complicating pregnancy and labor.

Treatment.—Progress in the treatment of ovarian tumors was to be looked for chiefly in the field of the malignant growths. The surgery of ovarian cancer has, however, altered little, if at all, and the beneficial effects of radiation have remained more a promise than an actuality. Improvement in the results of treatment has perhaps occurred, but inconsistencies in classification, differences of opinion on the histologic criteria of malignancy, and defects in follow-up organization have made statistics alleged to prove this point all but valueless.

Before considering the claims made for radiation therapy, it should first be noted that without it the cure rates as reported have varied from 9.5 per cent (Schleyer⁵¹) to 53.8 per cent (Norris and Murphy⁵¹). On account of this discrepancy in basic figures, no statistics using a five-year standard of cure are able conclusively to demonstrate the advantages of radiation. Nevertheless, isolated observations of the shrinkage of palpable tumors, following x-ray therapy and experiences with apparently hopeless cases in which the patients have recovered and lived well beyond the five-year period, indicate beyond doubt that in some instances at least radiation is an effective agent in treatment. Progress in this direction can only be made by meticulous histologic classification and its careful correlation with the effect of therapy. This is perhaps the direction that the advance of the next twenty years will take.

REFERENCES

- (1) *Abraham, E. G.*: Arch. f. Gynäk. 154: 565, 573, 1933. (2) *Bergstrand, H.*: Acta obst. et gynec. Scandinav. 13: 336, 1934. (3) *Brenner, P.*: Frankfurt. Ztschr. f. Path. 1: 150, 1907. (4) *Caylor, H. D., and Masson, J. C.*: AM. J. OBST. & GYNEC. 19: 45, 1930. (5) *Counsellor, V. S., and Broders, A. C.*: Ibid. 35: 642, 1938. (6) *Counsellor, V. S., and Wellbrock, W. L. A.*: Ibid. 28: 40, 1934. (7) *Fischel, A.*: Ztschr. f. d. ges. Anat. (Abt. 1) 92: 34, 1930. (8) *Föderl, V.*: Arch. f. Gynäk. 165: 392, 1938. (9) *Frankl, O.*: Arch. f. Gynäk. 131: 325, 1927. (10) *Furth, J., and Butterworth, J. S.*: Am. J. Cancer 28: 66, 1936. (11) *Geist, S. H.*: AM. J. OBST. & GYNEC. 30: 480, 1935. (12) *Glynn, E.*: J. Obst. & Gynaec. Brit. Emp. 28: 23, 1921. (13) *Halban, J.*: Arch. f. Gynäk. 124: 457, 1925. (14) *von Kahlden, C.*: Zentralbl. f. allg. Path. u. path. Anat. 6: 257, 1895. (15) *King, E. S. J.*: Am. J. Path. 8: 417, 1932. (16) *Klaften, E.*: Arch. f. Gynäk. 158: 544, 1934. (17) *Kleine, H. O.*: Zentralbl. f. Gynäk. 63: 2051, 1939. (18) *Lauche, A.*: Virchows Arch. f. path. Anat. 243: 298, 1923. (19) *Löffler, E., and Priesel, A.*: Beitr. z. path. Anat. u. z. all. Path. 90: 199, 1932. (20) *Maury, J. M., and Schmeisser, H. C.*: AM. J. OBST. & GYNEC. 27: 290, 1934. (21) *Melnick, P. J., and Kanter, A. E.*: Ibid. 27: 41, 1934. (22) *Mestitz, W.*: Arch. f. Gynäk. 130: 667, 1927. (23) *Meyer, R.*: Ztschr. f. Geburtsh. u. Gynäk. 77: 505, 1915. (24) *Idem*: Virchows Arch. f. path. Anat. 250: 595, 1924. (25) *Idem*: Zentralbl. f. Gynäk. 54: 2374, 1930. (26) *Idem*: AM. J. OBST. & GYNEC. 22: 697, 1931. (27)

A PROVISIONAL CLASSIFICATION OF OVARIAN TUMORS FOR 1940

Before outlining the classification which the work of the last twenty years appears to have led to, several principles which should govern any modern classification may be suggested.

1. Although it has been said for years that a classification based on histogenesis is not possible, most classifications have attempted to segregate groups which are histogenetically similar although the actual histogenesis may not be known. This principle should be continued.

2. The ancient division into cystic and solid tumors should finally be abandoned, since these gross characteristics have neither important diagnostic nor prognostic significance.

3. That practically all varieties of ovarian neoplasm have benign and malignant counterparts is now pretty evident, and this may well become an assumed vertical division of all true tumors of the ovary. This will make unnecessary the formal repetition of the entire list under both benign and malignant headings.

4. A prerequisite for any acceptable classification of ovarian tumors is that it represents as nearly as possible the general opinion of the time and not simply the private views of some individual theorist.

A CLASSIFICATION OF OVARIAN TUMORS

I. Dysfunctional cysts of the follicle and corpus luteum.

II. Endometrial cysts and endometriosis.

III. Primary neoplasms of the ovary.

A. Epithelial tumors.

1. Serous cystadenoma and cystadenocarcinoma.

Special type: Adenoid cystic fibroma (Frankl).

2. Pseudomucinous cystadenoma and cystadenocarcinoma.

Special type: Mucous fibroepithelioma (Brenner).

B. Connective tissue tumors.

1. Fibroma and fibrosarcoma.

2. Rare connective tissue tumors (Myoma, lymphangioma, etc.)

C. Teratomas.

1. Dermoid (cystic teratoma).

2. Complex (solid) teratoma.

Special type: struma ovarii.

D. Tumors arising from the specific cells of the gonad.

1. Granulosa cell tumor.

Special types: a. Folliculome lipidique (Lecene)

b. Theca cell tumor.

2. Arrhenoblastoma.

Special type: Testicular adenoma (Pick)

3. Dysgerminoma.

E. Doubtful tumors.

1. Endothelioma.

2. Hypernephroma.

3. Mesonephroma (Schiller).

IV. Metastatic tumors of the ovary.

THE CLINICAL ADVANCES OF TWENTY YEARS

Only one-tenth of this review remains to be devoted to the advances in the clinical field. This is not an unreasonable proportion, however, for the main features of diagnosis and treatment of ovarian tumors have

CERTAIN OUTSTANDING TRENDS IN GYNECOLOGY DURING THE PAST FORTY YEARS

ROBERT T. FRANK, M.D., NEW YORK, N. Y.

MY PERSONAL experience goes back forty years. In 1900, although gynecology was already a very active specialty, many technical developments were still in their infancy. For example, in that year, the question of whether the cervical stump remaining after supravaginal hysterectomy for fibroids should be buried, the uterine arteries separately ligated, or the cervical stump drained through the lower end of the abdominal incision was still in active debate, as shown by presentations and discussions taking place at the meetings of various specialist societies. Such well-known figures as Howard A. Kelly, Davenport, and E. Lapthorn Smith of Canada took part in this, and yet, Emil Ries of Chicago, Wertheim of Vienna and a few others, had successfully performed radical abdominal removal for carcinoma of the cervix several years previously.

During this same period, violent discussions were frequent as to whether acute salpingitis should be operated upon in the "hot stage" or allowed to go to the interval before operative intervention was undertaken. At operation it was also debated whether these patients should be drained abdominally. A number of lives were needlessly sacrificed by the less conservative surgeons who, without selection, routinely performed operations on acute pus tubes or even acute salpingitis.

The treatment of cystocele, rectocele, and prolapse was likewise in a very unsatisfactory state. Particularly the older group of operators was satisfied to resect the anterior and posterior mucosa for cystocele and rectocele and suture the superficial defects they had created, without regard for the underlying fascial and muscular structures. Prolapse was almost universally treated by ventrofixation in addition to vaginal plastic, although some operators utilized the round ligaments with the hope of giving additional support by placing the uterus in ante-flexion. The results with rectocele were much better than with cystocele. It was still the custom to perform multiple operations such as nephropexy with appendectomy (through the same incision), anterior and posterior colporrhaphy and ventrofixation at the same session on patients suffering from enteroptosis.

Although the technique of transabdominal operation was in the formative stage, many operators, in fact more than today, had developed great skill in the vaginal approach. This was due to the fact that until improvements in aseptic technique had rendered transabdominal section less dangerous, the mortality by the vaginal route was far smaller. Vaginal hysterectomy including removal of large fibroids by morcellation was frequently resorted to. Ovarian cysts and inflamed adnexa, as well as ectopic gestations, were successfully removed from below.

Idem: Arch. f. Gynäk. 148: 541, 1932. (28) *Moulonguet, P.*: In Les diagnostics anatomo-cliniques de Paul Lécène. Appareil génital de la Femme, 2: Paris, 1932, Masson et Cie., p. 308. (29) *Neumann, H. O.*: Zentralbl. f. Gynäk. 52: 2518, 1928. (30) *Norris, C. C.*: AM. J. OBST. & GYNEC. 1: 831, 1921. (31) *Norris, C. C., and Murphy, D. P.*: Ibid. 23: 833, 1932. (32) *Novak, E.*: Ibid. 22: 826, 1931. (33) *Idem*: Ibid. 36: 840, 1938. (34) *Novak, E., and Brawner, J. N., Jr.*: Ibid. 28: 637, 1934. (35) *Novak, E., and Gray, L. A.*: Ibid. 31: 213, 1936. (36) *Idem*: Ibid. 35: 925, 1938. (37) *Novak, E., and Jones, H. W.*: Ibid. 38: 872, 1939. (38) *Novak, J., and Wallis, O.*: Arch. f. Gynäk. 164: 543, 1937. (39) *Orthmann, E. G.*: Monatschr. f. Geburtsh. u. Gynäk. 9: 771, 1899. (40) *Pfannenstiel, J.*: Handb. d. Gynäk. (Veit), Bergmann, Wiesbaden, 1898 3: p. 239. (41) *Pick, L.*: Arch. f. Gynäk. 76: 191, 1905. (42) *Plate, W. P.*: Ibid. 153: 318, 1933. (43) *Plaut, A.*: Ibid. 153: 97, 1933. (44) *Idem*: AM. J. OBST. & GYNEC. 25: 351, 1933. (45) *Russell, W. W.*: Johns Hopkins Hosp. Bull. 10: 8, 1899. (46) *Sampson, J. A.*: Tr. Am. Gynec. Soc. 46: 162, 1921. (47) *Scheffey, L. C.*: AM. J. OBST. & GYNEC. 9: 490, 1925. (48) *Schiller, W.*: Arch. f. Gynäk. 156: 513, 1934. (49) *Idem*: Ibid. 160: 344, 1935. (50) *Idem*: Am. J. Cancer 35: 1, 1939. (51) *Schleyer, E.*: Monatschr. f. Geburtsh. u. Gynäk. 79: 302, 1928. (52) *Schmitz, E. F.*: AM. J. OBST. & GYNEC. 9: 247, 1925. (53) *Seegar, G. E.*: Arch. Surg. 37: 697, 1938. (54) *Traut, H. F., and Butterworth, J. S.*: AM. J. OBST. & GYNEC. 34: 987, 1937. (55) *Traut, H. F., Kuder, A., and Cadden, J. F.*: Ibid. 38: 798, 1939. (56) *Varangot, J.*: Lyon chir. 35: 448, 1938. (57) *Wolfe, S. A., and Kaminester, S.*: AM. J. OBST. & GYNEC. 27: 600, 1934.

hysterectomy, interposition of the uterus, and various abdominal or vaginal fixations. The use of the Manchester operation was still limited mainly to the English school.

In the interim, the gynecologic armamentarium as well as that of the rest of the profession had been greatly enriched by many new discoveries. I mention only a few: The Wassermann reaction enabled us to diagnose syphilis even in its latent stages. Blood transfusion, both by the direct and indirect method, robbed ruptured tubal pregnancy of much of its dangers. The discovery and the use of x-ray and of radium proved a boon in the treatment of menorrhagia, of certain uterine fibroids, and of carcinoma of the cervix. A real renaissance of physiotherapy developed, applicable in gynecology to the treatment of chronic adnexal diseases. Endocrinology, which later on was to grow and spread with the rapidity of a weed, was still a modest bud just poking its head above ground and yet attracting the interest of those in search of the new and promising. Over-optimists were already recording wonder cures with "endocrine products," since proved to be inert and now relegated to oblivion.

World-wide movements for promoting and popularizing the practice of contraception, antenatal care, recognition of early cancer were developing and helped to educate the laity. With all due modesty, we may state that the gynecologist continued to stay in the van of progress, fully utilizing the nova available.

A survey of the present must lack perspective and, therefore, proves difficult, and in the light of tomorrow, perhaps misleading.

The trend during this last decade, at least for the intellectually honest and best informed, is largely away from operative measures. This applies, for example, to the treatment of carcinoma of the cervix in which radiation therapy by means of x-ray and radium has displaced surgery except in the hands of a few. Carcinoma of the corpus uteri, however, is still treated mainly by hysterectomy. In the treatments of fibroids of the uterus, the indications between the choice of operation or radiotherapy have become clear-cut and well defined, based largely upon the findings during preliminary exploratory curettage.

A great improvement has taken place in the early cure of gonorrheal diseases and some of the more newly classified venereal infections such as lymphogranuloma and granuloma venereum. Complete cure of gonorrhea in its earliest stages, before it has reached the tubes and peritoneum, can be obtained by hyperthermia. By means of chemotherapy with sulfanilamide and its congeners, not only gonorrheal but also streptococcal infection has been arrested and cured in both the early and later stages of the disease. In consequence, the well-trained gynecologist limits operation to chronic recurrent adnexal inflammations.

For the cure of prolapse, the English Manchester (Donald, or misnamed Fothergill) operation has made major strides in the United States and promises to displace other techniques in the near future.

Mechanical (tubal) sterility can now be recognized or excluded by means of Rubin's insufflation test, and the location of atresias or stric-

In passing, I should mention that the question as to whether a ruptured ectopic pregnancy should be operated upon in the tragic stage was as yet an open one. This was largely due to our inability to restore exsanguinated patients by means of blood transfusion, the sole available remedies consisting of intravenous normal saline solution, exaggerated Trendelenburg position, bandaging of the extremities, and sedation for shock.

The treatment for sterility and dysmenorrhea was on the whole purely mechanical. Opening of the cervical canal by the Pozzi procedure and straightening of the canal by means of the Dudley operation were the rage. No means of recognizing tubal obstruction were available except by opening the abdomen. The stem pessary was freely employed for the relief of dysmenorrhea, sometimes followed by severe pelvic infections. A few pioneers experimented with Fliess's method of cauterizing the nasal mucosa to relieve dysmenorrhea.

In the same year, 1900, A. W. Johnstone, apparently unchallenged, spoke as follows at a meeting of the American Gynecological Society: "There is not one iota of proof that the ovary has any other function than the manufacture of eggs." Eleven years later, such authorities as J. M. Baldy and J. Monro Kerr, still voiced somewhat similar sentiments.

In the second decade of the twentieth century, a great change in viewpoint is noted. Purely mechanistic concepts were in part replaced by greater reliance on a foundation of pathology. A number of voices were raised modestly in the wilderness in favor of a more physiologic point of view. This evidently was sensed by Dr. Robert L. Dickinson when he delivered his presidential address before the American Gynecological Society in 1920. He referred to the gynecologist as follows: "Surgery we have promoted. But if we be just surgeons, by surgeons we may be displaced." The gynecologist need not blush for the advances that he has inaugurated before and since 1920; these advances are of the utmost importance in every branch of medicine.

In the intervening twenty years between 1900 and 1920, technical procedures were standardized. The well-trained gynecologist the world over performed supravaginal hysterectomy for fibroids, radical hysterectomy for carcinoma of the cervix, removal of ovarian neoplasm, salpingectomy or salpingo-oophorectomy for ectopic gestation, as well as other intra-abdominal operations in almost identical fashion. There remained few if any who still advised operation for adnexal diseases in the acute stage.

During the search for improvement in the relief of cystocele, rectocele, and prolapse, intensive study of pelvic anatomy had progressed. Two schools of thought resulted: The one relied mainly on muscular support (the levators and the perineal muscles); the other concluded that the fascial and connective tissue strands (base of the parametria, pubocervical tissues) gave the main support. In consequence of these anatomic researches, the operations practiced for prolapse included sutures of the levator plates, shortening of the parametria, vaginal

AN EVALUATION OF THE TREATMENT OF UTERINE CANCER

WILLIAM P. HEALY, M.D., NEW YORK, N. Y.

IN REVIEWING the developments in the field of uterine cancer in recent years, they would seem to fall in two major groups: one dealing with diagnosis, the other with treatment.

Cullen in 1909 in the preface to his splendid work on *Cancer of the Uterus* said: "The number of cases of cancer of the genital tract coming too late for operation is so appalling that the surgeon is ever seeking to devise ways and means by which the dread malady may be more generally detected at the earliest possible moment—at a time when complete removal of the malignant tissue is still possible."

Only in recent years, one might say since the establishment of the American Society for Cancer Control, has any well-organized and continued effort been made to reach the lay public and to impress it with the character of such symptoms as may indicate the presence of cancer and the urgent need of prompt medical examination in order that the disease may be detected if present. Despite opposition to these publicity campaigns from within and without the medical profession, largely based on the assumption that much "cancerphobia" would be established and little good accomplished, the work has gone on and the American Society for Cancer Control now is acknowledged as a vital force of great value in its chosen field.

As a result of this publicity a large part of the public has become cancer conscious, and it has been comparatively easy to educate its members to the value of periodic medical examinations at intervals of a year or less.

Equally as important to the patient and the gynecologist has been the need of educating the medical practitioner in the essentials of a thorough investigation of the patient's symptoms, including, when possible, inspection, palpation, instrumentation and last but not least removal of a portion of any suspected lesion for microscopic study.

One would be rash indeed to state that either the public or the medical profession is fully alive to its responsibilities in this regard. Nevertheless one is inclined to believe that "early diagnosis," the first of the essentials in a proper approach to the cure of a patient with uterine cancer, is now better understood and more quickly and logically sought, especially by the general practitioner.

In an effort to help solve the cancer problem, several institutions dealing exclusively with cancer have been established in this country and, equally as significant, so-called "tumor groups" made up of a small cross section of the visiting staff have been formed in many hospitals to further the study of cancer.

Moreover recently the federal government has entered the field, established an Advisory Cancer Council, and funds have been as-

tures determined by uterosalpingography with harmless water-soluble and readily absorbed radio-opaque media.

The preoperative diagnosis of functionally active ovarian tumors is now feasible based on their clinical symptoms or the biologic changes they produce. These growths include arrhenoblastoma, granulosa, and theca cell tumors, all of the ovary, as well as chorionepithelioma, wherever it may originate or metastasize.

Endocrinology has become an important discipline of medical science. In the development of this branch of medicine, gynecologists have taken a prominent part. It is now accepted that functional diseases of the female may originate not only in the ovary but also in the pituitary, adrenal, or thyroid glands. Our point of view concerning the significance, importance, and treatment of functional amenorrhea, bleeding, sterility, and dysmenorrhea has been entirely revised, but doubtless will undergo much further revision before stabilization is arrived at. In bleeding, for example, the uterine mucosa is regarded merely as a labile and changeable indicator of ovarian and other endocrine activity. Much advance can be recorded in the recognition of underlying causes which produce these functional disturbances.

Treatment is in a most chaotic stage; this, in spite of the fact that pure crystalline estrogens, progestational products, and androgens are now available, supplemented by a host of similarly acting synthetic products. The gonadotropic substances remain in an impure state and are as yet of little practical value. Striking results in the treatment of the menopause have been obtained. The huge and cumbersome literature, particularly that of purely clinical nature, which has been accumulating rapidly, will doubtless eventually be forgotten.

The advances of the last twenty years have been aided by a tendency toward accuracy and control, as shown by reliance on investigative machinery, by the employment of rigid statistical methods, by the development, with the aid of physiologists and biochemists, of standardization of bio-assay and chemical assays. The employment of primates, particularly the higher monkeys, in some researches, has made application of the results obtained more readily transferable to the human being.

What advances the future has in store, I would not venture to predict. That gynecology and the other branches of medicine steadily will progress seems assured.

Bonney reports that the regional lymph nodes were carcinomatous in 42 per cent of his operable cases, and he states that about one in five of such cases survived five years and that the operative risk in these cases was 20 per cent as against only 10 per cent where there was no regional lymph gland involvement.

Bonney's paper read before the American Gynecological Society in 1935, in which he gave a critical review of his experience with the Wertheim operation covering a period of twenty-eight years from 1907 to 1935, may be regarded as representing the best that can be obtained by modern surgical methods associated with a high degree of surgical skill.

It is significant that over a period of 28 years this distinguished surgeon of high repute had performed the radical operation only 483 times. He states that on the average his operability percentage was 63, in other words 37 per cent of his cases required some other form of treatment than surgical. His total five-year operative salvage of all cases seen was 24.6 per cent.

In 1898, about the time that Ries, Clark, Wertheim and others were devising more and more radical operative procedures, the Curies announced in Paris their discovery of radium. This event regarded at the time as of outstanding scientific importance, ultimately became of the utmost significance in the world of medicine. Three years earlier the roentgen ray had been discovered.

Both radium and roentgen rays were promptly and enthusiastically subjected to rigid scientific study and experiment. In a short time as Burnam says "the relationship between the artificially produced roentgen rays and the spontaneously emitted radium rays, suspected from the beginning, had been adequately proved."

Many chemical and biologic investigations, especially those dealing with the effects of the new rays on living matter were soon published. Outstanding among these investigators was Dominici, whose studies of the histologic changes observed after irradiation in normal and neoplastic tissues established a solid groundwork for the views held today. He concluded according to Burnam "that the tolerance to rays was definitely associated and proportional to the approach to complete adult and highly differentiated states, and that the more undifferentiated and embryonic the tissues were, the less their capacity to tolerate radiation and, conversely, the greater their sensitivity to injury."

By 1909 radium was in use clinically for the treatment of many neoplastic conditions, including uterine and cervical cancers. Its palliative effects in controlling hemorrhage, discharge, and pain were fully recognized. However, with the exception of a small amount of radium in the possession of Dr. Robert Abbè, a New York surgeon, there was little or none available for clinical use in this country.

It was particularly fitting therefore that the pioneer in exploiting the clinical application of radium rays in the treatment of human cancer in America should be one of its outstanding teachers, and

signed for clinical and research fellowships. All this indicates an awakening of a substantial and constructive nature to the requirements of the problem and is most encouraging.

The almost utter hopelessness of the surgical prognosis in cancer of the uterine cervix at the opening of the present century may be judged by Cullen's statistics of patients under observation and treatment at the Johns Hopkins Hospital from 1893 to 1899 inclusive. He reports a total of 141 patients, in 73 of whom the disease was regarded as operable, and an attempt at surgical cure was made. Four of these patients survived five or more years, a cure rate of 5.5 per cent. In the remaining 68, only curettage was done, and the duration of life thereafter must have been brief. Thus there was in this series of 141 cases of cancer of the cervix a total five-year salvage by surgical methods of 1.6 per cent.

In 1900 and 1901 Wertheim published his papers describing a radical type of abdominal hysterectomy for the operable cases of cervical uterine cancer. These papers created at the time a great deal of discussion and were more or less enthusiastically received. A most important feature of his operation lay in a wide excision of the parametrium. Wertheim also emphasized the frequency of involvement of the pelvic lymph nodes by metastatic cancer as he found them in about one-third of his operable cases. It soon became evident that the radical abdominal hysterectomy of Wertheim extended the field of operability in cancer of the cervix. In its essential features it consisted of a wide excision of the parametria, a low amputation of the vagina and removal of the pelvic lymph nodes. In the removal of the parametria, the ureters were laid bare, and often either accidentally injured or their circulation interfered with so that necrosis and leakage subsequently occurred.

Wertheim's percentage of three-year cures and later on, five-year cures, obtained by his procedure were so much better than any previously obtained by surgical methods that there was prompt recognition of the merits of the procedure, and it was widely taken up by gynecologists.

From the first it was realized that great surgical skill was required to perform properly the operation. Gynecologists soon discovered that there were not enough operable cases to permit more than a few of them to develop a satisfactory surgical technique. The mortality associated with the operation was unduly high. Wertheim was said to have had a 30 per cent mortality in his first 100 operations, and Bonney, a more modern and highly efficient technician, reports a 20 per cent mortality in his first 100 cases. The question soon arose as to whether removal of the pelvic lymphatics held out much additional hope of permanent cure.

Wertheim in his early reports stated that the disease had recurred in all cases in which he found the lymph nodes involved at the time of operation, therefore he regarded their removal as of prognostic value only.

2. End results or percentage of cures in favorable cases are superior to those obtained by operation.

3. Primary mortality under radiation should not exceed 1 per cent for all types of cases, whereas primary surgical mortality is from 10 per cent to 20 per cent in the favorable cases, treated by the Wertheim operation.

4. Not over 25 per cent of the cases of cervical cancer can be regarded as favorable for surgical intervention. This makes it difficult for more than a very few surgeons to attain the operative skill necessary to perform successfully the radical operation, but unfortunately not all of the favorable cases could reach such surgeons.

5. In the past twenty-five years, the teaching and training of radiologists has progressed with unparalleled speed so that there are special societies with large membership rolls, sections of the state and national societies, a radiologic examining board and also a College of Radiology.

6. As a result radiologists competent to treat the early or favorable as well as the advanced or hopeless case of cervical cancer are to be found in almost every community. It may not be amiss at this point to quote from the closing remarks of Mr. Bonney in the discussion of his paper referred to above: "One cannot look into the future, but I think it is quite possible that we shall one day see the end of surgery as a treatment of carcinoma of the cervix."

Carcinoma of the uterine body likewise has presented a fertile field for radiation therapy. In the beginning there was considerable opposition to its use as it was felt that surgical procedures were in themselves adequate to care for the disease, and besides there was a strong feeling supported by many investigators that adenocarcinoma was not a radiosensitive tumor. However, since carcinoma of the uterine body is a post-menopausal disease, many of the patients were old or feeble, therefore poor risks for major surgery, and other patients declined operation. Radium alone or combined with roentgen ray was the only form of therapy available for such cases and in many instances was used. As a result, considerable evidence gradually accumulated to indicate that radiation methods could establish in carcinoma of the corpus not only palliation of symptoms but permanent cure of the cancer.

Even more significant was the information obtained by studying the histologic structure of the tumors and comparing this with the response to the rays. As in carcinoma of the cervix, it was found that certain types were more sensitive and others more resistant. The less differentiated and more malignant the cell structure the more radiation sensitive the tumor often seemed.

Critical studies of series of cases of cancer of the corpus treated by radiation and surgery seemed to indicate that there are two major histologic groups, one of rather low malignant quality known as adenoma malignum in which panhysterectomy by the vaginal or abdominal route may be expected to establish a permanent cure. The

gynecologists, Dr. Howard A. Kelly, a distinguished surgeon and technician, Professor of Gynecology at the Johns Hopkins Medical School.

As more and more experience was gained by clinicians throughout the world in radiation therapy, it became evident that the old conception of cancer as a single disease must be changed. It soon was realized that cancers grossly similar and, apparently identical, often behaved quite differently under irradiation. These observations led to an appreciation of Dominici's earlier histologic studies and a realization that a new classification of cancers could be made based largely on their response to radium or roentgen rays. In other words, some cancers located in certain parts of the body or possessing a certain type of histologic structure might be radiosensitive and thereby would tend to disappear more or less completely and permanently under irradiation. Cancers which failed to show much response to radiation were designated radioresistant.

Gynecologists were among the first to use radium for the treatment of internal cancer, especially cancer of the cervix, as so many of the patients were in an advanced stage of disease when first seen, and even a radical Wertheim operation seemed inadvisable. Soon it was recognized that cancers of the cervix responded quite well to radiation therapy and on the whole must be regarded as radiation sensitive.

In the meantime Broders and others published classifications of epidermoid carcinoma in which the cases were divided into three grades, depending upon variations in histologic structure. The degree of histologic malignancy in these tumors was lowest in Grade I and highest in Grade III. Studies began to appear from radiation therapists, indicating that the radiation sensitivity of the epidermoid tumors, and especially the cervical carcinomas, was lowest in the fully differentiated Grade I cancers and highest in the most malignant or Grade III varieties, so that radiation therapists were able to obtain equally as good end results in the treatment of their cases regardless of the histologic grade of malignancy; whereas studies of large series of patients treated by operation alone, in such outstanding institutions as Johns Hopkins Hospital and the Mayo Clinic, indicated that those patients with cervical cancers in Grade II and Grade III seldom survive five years.

It is quite evident that the entire picture of carcinoma of the cervix histologically, clinically, and therapeutically, as we understand it today, has been created by the discovery of radium and the subsequent developments in the field of radiotherapy. An individual surgeon here or there may still adhere to surgical measures, but throughout the world and especially in all large teaching centers where modern methods of radiation therapy are available they have displaced surgery in the treatment of carcinoma of the cervix. The reasons are obvious:

1. Radiation methods are applicable to all cases.

PUERPERAL INFECTION

B. P. WATSON, M.D. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., F.R.C.O. & G.,
NEW YORK, N. Y.

THE last twenty years have been marked by notable advances in our knowledge of puerperal infections. These have resulted in a better understanding of the underlying factors leading to infection, of the behavior of the infecting organisms, and of methods of treatment. Already this added knowledge has led to the practical result of lowering both the incidence and the case mortality of the disease.

Twenty years ago it was recognized that the aerobic hemolytic streptococcus was only one of the organisms which might cause puerperal infection, that other organisms were responsible for many cases, and that among these the anaerobic streptococcus played an important role. It is during this period, however, that the two types of infection have been clearly defined and differentiated.

It is forty-five years since Kroenig first described a case of puerperal infection from which he recovered an anaerobic streptococcus. In 1910 Schottmüller described similar cases and named the organism *Streptococcus putridus*. In 1921 Curtis found these organisms in certain cases of pyosalpinx. Then came a series of observations of Schwarz and Dieckmann, and by Harris and Brown in this country, and later by Colebrook in England, confirming the part played by the anaerobic streptococcus in puerperal infection. Schottmüller had already described the characteristic clinical picture: Irregular fever, fetid lochia, thrombophlebitis, not infrequently positive blood culture, occasionally lung abscess. As anaerobic cultures have become a routine in the investigation of cases of fever in the puerperium, it has become evident that a majority of these cases are due to the anaerobic organism. Studies show that this type of infection is most likely to supervene in patients whose tissues had been much traumatized by the delivery, who have lost much blood, who are shocked, or who have had ruptured membranes a long time prior to delivery. It is now known that the infection is practically always an endogenous one, that the organisms exist in the vagina previous to delivery, that they are ordinarily innocuous to the individual, and that it is only under the conditions above mentioned that they are liable to lose their saprophytic character and become pathogenic.

These facts have given us a definite scheme of prophylaxis, viz., the avoidance in every way possible of the long labor, of the traumatization of tissue by forceful vaginal delivery, of excessive blood loss, and, if this is unavoidable, its immediate treatment by blood transfusion. Delay in the performance of cesarean section after labor has begun or the membranes have ruptured predisposes to this type of infection.

The role of vaginal antiseptics during labor is still a matter of doubt. There are those who believe that they may be effective but the majority

other of higher malignant histologic character in which hysterectomy gives poorer end results than when radiation alone is used or radiation followed by hysterectomy.

It would appear therefore that the discovery of radium in 1898 by the Curies has changed for the better the entire therapeutic picture in uterine cancer and has to a large extent displaced or superseded surgical measures in the treatment of cancer of the cervix.

This situation has compelled gynecologists to acquire a knowledge of radiation and radiation methods as applied to the treatment of uterine cancer. As a result many gynecologic clinics have assigned one or more members of their staff to the care of the malignant tumor cases, and these individuals have taken special courses and undergone special training for this purpose. It is highly desirable that all patients suffering from uterine cancer, either of the corpus or cervix, should remain under the supervision of the gynecologist throughout their course of radiation therapy, since the complications that may occur almost invariably require surgical attention. In other words, the gynecologist should always assume full responsibility for his patients' care and carry out the radiation therapy if he is, by training, competent to do so. If not he should work in close cooperation with an expert radiologist.

to the Lancefield classification clinicians were puzzled by the fact that in about 3 per cent of women a hemolytic streptococcus could be recovered from the vagina or cervix in the later part of pregnancy and in labor, and that practically none of those women ever exhibited symptoms of infection in the puerperium. It was thought that these women had acquired an immunity to their own organisms. In the last five years investigation of these vaginal streptococci, by the Lancefield and other techniques, has shown that these organisms do not belong to Group A and are, therefore, really nonpathogenic for all human beings. Since typing of these vaginal streptococci has been systematically done in our Service, not a single Group A organism has been found. It must, therefore, be concluded that in the vast majority of cases of streptococcal infection the organism is introduced from without. Since the streptococcus responsible for puerperal infection is the same organism that causes other varieties of disease such as tonsillitis, otitis media, pneumonia, erysipelas, scarlet fever, etc., it is evident that the parturient and puerperal woman may be infected by contact, either direct or indirect, with such cases. That the infection is usually carried indirectly through "carriers" has been definitely proved. These carriers may or may not have been in contact with infected patients, usually they have not. The organism is most commonly present in their mouths, throats, or noses, and is, apparently, harmless to the individual. As in the case of the vaginal streptococcus, that found in the throat may be other than Group A and, therefore, harmless. Of 103 students examined during the past year, 17 proved to have streptococci in the throat or nose but only one of these was in Group A. Of 242 nurses examined, 30 showed hemolytic streptococci and only 3 of these belonged to Group A.

One of the first to call attention to the importance of the carrier was Meleney, who in 1926 showed that a series of streptococcal infections in surgical wards was traceable to certain streptococcal carriers in the operating room.

Two years later, in the Sloane epidemic of 1927, he proved that organisms of infected patients were serologically identical with those recovered from the nose and throat of certain individuals of the nursing and medical staffs. Since then a mass of evidence has accumulated, definitely establishing this relationship between carrier and patient. One of the most notable observations was that conducted by Kinloch, Smith, and Stephen in Aberdeen. This knowledge has made possible a most important prophylaxis against this type of infection, namely, the exclusion from contact with parturient or puerperal women of all such carriers. The detection of these carriers involves regular periodic cultures of the nose and throat of each attendant and the exclusion of individuals who prove to be positive. As an additional safeguard, the complete masking of the nose and throat of doctors, nurses, and attendants on the parturient and puerperal patient is essential. This technique is now carried out in every well-conducted clinic in the country and must be responsible for a diminution in the incidence of infection.

of those who have investigated the matter are frankly skeptical. Indeed Colebrook has gone so far as to state that after the use of vaginal antiseptics the vaginal flora is actually increased.

So far no specific drug has been found which will act on this organism as does sulphanilamide on the hemolytic streptococcus, but the progress made in the discovery of variants of sulphanilamide which are effective against other organisms holds out hope that one may yet be found which is more or less specific against these anaerobes.

It is now established beyond a doubt that the anaerobic streptococcus is the most frequent organism present in cases of septic incomplete abortion. This has led to a modification in the treatment of these cases in the last few years. Twenty years ago most of us advocated and practiced ultraconservatism in the treatment of these cases, recognizing excessive hemorrhage as practically the only indication for the emptying of the uterus in the presence of fever. Today a large number of clinics are carrying out prompt evacuation of the putrid uterine contents as soon as culture has demonstrated the absence of a hemolytic streptococcus. The result has been a great curtailment in the duration of the fever and a marked shortening of the time of hospitalization of the patients, with no added mortality.

Our knowledge of the aerobic hemolytic streptococcus has been enormously extended in the last twenty years. This type of infection was the first definitely established on a scientific basis. It may be recalled that micro-organisms were first demonstrated in the lochia of infected women by Meyerhöfer in 1863, and in the blood of infected women by Coze and Feltz in 1869. They described the organism as a coccus occurring in chains. Ten years later Pasteur with his collaborators cultivated these organisms and definitely determined that they were the cause of the infection. For many years thereafter it was thought that this streptococcus was the sole cause of puerperal infection and that it was a specific organism with no variants. Over thirty years ago bacteriologists began to recognize that the aerobic streptococcus could be divided into a series of groups. One of the most important of these subdivisions was that which differentiated between the hemolytic and the nonhemolytic organism. It was at the same time proved that the hemolytic organism was the more virulent of the two. For many years thereafter there was no differentiation of the hemolytic organisms; all were regarded as pathogenic in the human subject. Then came the work of Lancefield and others, who showed that the hemolytic organisms could be differentiated into several groups which were named A, B, C, D, etc. All of these strains may be recovered from the human subject but only those belonging to Group A cause serious infection. This hemolytic streptococcus Group A is now recognized as the organism responsible for a great variety of diseases, including puerperal sepsis. It is the organism responsible for the great epidemics of the past, and for the sporadic cases and minor epidemics which still occur today.

Infection with the Group A beta hemolytic streptococcus is practically always exogenous in origin in contrast to infection with the anaerobic streptococcus which is practically always endogenous. Prior

it is a standard method of treatment for all types of puerperal infection and is used from the onset of the disease. There can be no doubt as to its beneficial results when so employed.

To sum up we may say that in the last twenty years definite advance has been made along the following lines:

1. Recognition of the part played by the anaerobes in puerperal and postabortal infection.

2. Proof that these anaerobic infections are endogenous in origin.

3. Proof that such infections are predisposed to by shock, hemorrhage, prolonged labor, and traumatization of tissue.

4. Realization that the removal of dead and decomposing material resulting from this type of infection can, in most instances, be effected with no risk, and usually with great benefit to the patient.

5. Identification of different groups of the beta hemolytic streptococcus and proof that only Group A is virulent in the human subject.

6. Establishment of the fact that infection with this organism is practically always exogenous.

7. Proof that these organisms are usually conveyed to the patient by a carrier who harbors them in mouth, nose, or throat.

8. Demonstration of the fact that the risk of infecting patients is practically annulled by periodic nose and throat culture of all the members of the obstetric staff and elimination of those who are carriers, and by the complete masking of the nose and mouth of all those who are attendant upon the parturient and puerperal woman.

9. Demonstration of the persistence of the organisms in the environment of an infected individual even for long periods after her removal therefrom.

10. A recognition of the necessity for most complete isolation of all such infected individuals and for proper provision for this in every maternity service.

11. The discovery of the beneficial effects of sulphanilamide and its derivatives in streptococcal, gonococcal, and *Bacillus coli* infections.

In the Sloane epidemic of 1927, the noses and throats of the carriers were the only sites in the environment of the infected patient from which organisms were recovered. It was, therefore, concluded that the organism would not survive for any length of time outside the human body.

Some years later, however, Dr. Elizabeth White, working with Colebrook at Queen Charlotte's Hospital in London, recovered the organisms from the dust of rooms occupied by infected individuals, and this even after a considerable period of time had elapsed since the patient was removed from the room. Her findings have been confirmed. This fact has re-emphasized the great importance of complete isolation of infected individuals and of thorough disinfection of the rooms which they have occupied and also of the contents of the rooms. It has re-emphasized the necessity for a separate and distinct isolation unit in every maternity service; the danger to obstetric patients if they are delivered in a room where general surgical work is done, and the danger to which the puerperal patient may be exposed if she convalesces in a ward or room in the immediate vicinity of infected individuals.

The detection of a single case of hemolytic streptococcal infection now calls for immediate and complete isolation of that individual and a thorough bacteriologic examination of everyone who may have come in contact with her. If such precautions are taken, no epidemic of any major character should be possible in the future. Our own experience is that hemolytic streptococcal puerperal infection is a rarity today, and we cannot but believe that the lowered incidence, as compared with twenty years ago, is, at least partly, due to these simple precautions.

Along with these advances in prophylaxis has come a most notable addition to the treatment of the disease. It is just five years since prontosil was demonstrated to have a notable effect in experimental, hemolytic streptococcal infections in mice. This observation was made by Domagk, in Germany. One of the first to follow up this observation in clinical work was Colebrook in London. He administered prontosil to patients with hemolytic streptococcal infection with startlingly beneficial results. Since then it has been demonstrated that sulphanilamide, a derivative of the original prontosil, has a profound effect on all types of hemolytic streptococcal infections, of which puerperal infection is just one. As with all new remedies its use has been rather indiscriminate. The rational mode of employment would seem to be to administer it to every patient with definite evidence of puerperal infection, to take cultures immediately and only continue the drug if a hemolytic staphylococcus, *Bacillus coli*, or gonococcus is found to be present. In cases of a staphylococcus infection sulphathiazole has been found to be effective. The advances made in chemotherapy for infections have been so spectacular in the past five years that there appears to be ground for hope that still further progress will be made in the immediate future. In connection with therapy, mention must be made of blood transfusion. Twenty years ago blood transfusion was still regarded as something to resort to only when all else had failed. Today

willing to testify. Education on this point is a vital necessity in the campaign against cancer of the uterus, a campaign in which every practitioner can play a part.

So far, I have said nothing as to the most characteristic of all menopausal symptoms, and, in fact, the only ones whose menopausal genesis will be conceded by all. I refer to the vasomotor group of symptoms, embracing the typical hot flushes which characteristically involve the head, neck, and the upper part of the thorax; the less frequent hot flushes which may involve the whole body; and the frequent sweats, which usually, but not always, are associated with the flushes, which they not infrequently immediately follow. This group of symptoms is definitely objective. The flushes, for example, can be seen and counted. They are definitely due to the hormone changes which characterize the menopause, although even these symptoms are influenced to some extent by emotional and psychic factors, through the link-up between the endocrines and the higher centers.

On the whole, however, these vasomotor symptoms offer the best criterion as to the severity of the climacteric and as to the efficacy or inefficacy of therapeutic measures. For the average practitioner, they will serve as a more readily available guide to therapy than the study of vaginal smears, useful though the latter may be to those taking the trouble to familiarize themselves with the comparatively simple technique.

So much stress has been placed by some upon the control of therapy by vaginal smears that the average practitioner is likely to believe that this procedure is essential to the intelligent management of the menopause, which I do not believe to be the case. It should be remembered, also, that there is no essential parallelism between the character of the vaginal smear and the degree of relief afforded by estrogenic therapy. For example, the symptoms are not infrequently relieved when there is little or no change in the smear.

Aside from the vasomotor phenomena, there is little doubt that the endocrine readjustment of the menopause may in some cases be the direct cause of such symptoms as headache, vertigo, and nervous instability. More often, however, the latter would seem to be of secondary nature. If, for example, a woman approaches the menopausal era with apprehensiveness, and if she begins to experience vasomotor symptoms which often disturb her rest at night, what is more natural than that she should become irritable and depressed; and develop headache and other symptoms, just as she would with any functional nervous disturbance. When the headaches are definitely periodic, occurring just before or during a menstrual period if the woman is still menstruating, or at approximately four-week intervals, if the periods are skipped or have ceased entirely, the evidence for an endocrine (pituitary) origin is much stronger, and headaches of this sort are almost always amenable to adequate estrogenic therapy.

The immediate cause of the menopause is a cessation of ovarian function. This statement can be made without equivocation now, although at one time it was thought possible that the explanation might lie in the fact that the cessation of ovarian function might be merely sec-

THE MANAGEMENT OF THE MENOPAUSE

EMIL NOVAK, M.D., BALTIMORE, MD.

WE HAVE learned much within the past generation as to the physiology, and especially the endocrinology, of the reproductive cycle, and this new knowledge has given us a better understanding of the nature and significance of menstruation and the various menstrual disorders, including also the menopause. Inevitably, though slowly, a smattering of this newer viewpoint has seeped through to the laity, so that the folklore concepts of a former day are less generally prevalent than they once were. To say that they have been dissipated would be glaringly incorrect, as every practicing physician knows. For example, there are still many women, not always of the ignorant group, who believe that the "change of life" entails a profound change in their life activities, and that the woman must at this dreaded epoch run the gauntlet of certain grim specters, such as mental breakdown, cancer, and the loss of sex attractiveness to her husband.

Even women who are better informed are wont to ascribe almost any subjective symptom which occurs after the age of forty to the oncoming menopause, and it cannot be fairly denied that some of our own profession innocently foster such wrong ideas by too ready acquiescence in such explanations. Too often it is an easy way out in the management of troublesome headaches, vertigo, nervous instability, anxiety neuroses of one sort or another, and many other symptoms which may have no relation whatsoever to the menopause. The woman who begins at the age of forty to excuse her vagaries on the "change of life" basis may not cease to menstruate until the age of fifty, this constituting a fairly effective refutation of her hypothesis.

There can be no doubt that in dealing with women as a whole we must take cognizance of this still heavy substratum of wrong concepts as to the significance of the menopause. The practical point from the physician's standpoint is that the easy assumption of menopausal etiology of symptoms in women of the fifth decade of life may lead him to overlook the real cause of these symptoms. Often they are explainable more rationally as the result of the stress and strain resulting from the rearing of large families of children, or because of domestic, economic, or marital problems, sometimes because of genuine physical disease. To give such a woman "shots" of estrogenic substance is a short cut for the doctor, but it is quite sure to bring the woman little relief in her difficulties.

But there are other wrong concepts, and other possibilities of mismanagement which may even spell death to the woman. The most glaring example is the belief of many women that abnormally excessive or irregular menstruation is to be looked upon as a normal manifestation of the menopause. This prevalent fallacy has been the direct cause of death for innumerable women, as every gynecologist will be

first two decades of the present century was of little or no value except for its psychic effect upon the patient. This method of treatment was begun at the old Landau clinic in Berlin in 1896, simply on the basis of an assumed analogy with the thyroid; for some years previously Murray and others had shown the brilliant results of thyroid therapy in the treatment of thyroid deficiency states. Curiously enough, at this time there was no knowledge of an internal secretory function of the ovary. But the great wave of ovarian therapy had been started, and billions of expensive tablets and capsules of ovarian substance were consumed by millions of trusting women in these early days of organotherapeutic enthusiasm. And now we know that these various organ extracts were inert or, at best, that they contained only negligible quantities of the ovarian hormones. It is a sad commentary on our profession that even our high-grade pharmaceutical houses feel it necessary still to continue the manufacture of these same old preparations today, simply because they are still prescribed by many of our profession.

For this practice there would seem to be no excuse today, since we now have available preparations of both ovarian hormones, and since these are unquestionably potent both experimentally and clinically. The advance in this field has been a very genuine one. The exact composition of both ovarian hormones is known; they can be prepared synthetically; they can be isolated in crystalline form; and we have learned much concerning their physiologic effects. In short, we can handle them just as we do the better understood drugs. Moreover, most of the estrogenic preparations on the market are trustworthy, in that they contain what they purport to contain. Why any physician can still cling to the use of the older forms of ovarian or corpus luteum tablets is difficult to understand, and more difficult to justify.

With reference to the methods of estrogenic therapy in menopausal cases, the first point meriting emphasis is that the great majority of menopausal women require no endocrine treatment at all. Many a woman passes through the menopause without "batting an eye," others have only mild vasomotor symptoms, and only a comparatively small proportion are made so miserable that endocrine therapy is necessary for relief. It is obvious that the mental attitude of the patient and the degree of endocrine enthusiasm of the attending physician will influence the frequency with which hormone treatment is resorted to. I have already stressed the very great importance of reassuring the patient and explaining to her in simple language what the menopause means and what it does not mean, as well as of correcting so far as possible any detrimental environmental factors which may exist.

In the minority of cases in which vasomotor symptoms are very severe, in which, for example, flushes and sweats occur fifteen or twenty times a day and so frequently during the night that the patient's rest is seriously disturbed, my experience is that nothing yields such beneficial results as estrogenic therapy by the hypodermic (intramuscular) route. The dosage must be adjusted according to the severity of the symptoms and the degree of response. In a case of average severity an injection of 10,000 international units of a good estrogenic

ondary to cessation of pituitary function. However, it is now established that the break in the endocrine chain occurs primarily in the ovary. The latter, in other words, reaches the end of its functional life span at the menopause, and beyond this is refractory to any form of pituitary stimulus.

Since the pituitary continues to function beyond the menopause, it would be expected that the characteristic hormone changes of the menopause, as determined for example by assay of the urinary hormones, would be a disappearance of estrogenic hormones and an excess of the gonadotropic principles, and this is exactly what occurs. The gonadotropic excess is demonstrable for many years beyond the menopause, the follicle-ripening principle predominating, but the luteinizing hormone has also been demonstrated in some cases. The disappearance of estrogen is not invariable, and this hormone has been found in the urine of some women long after castration. The postmenopausal occurrence of estrogen has not yet been satisfactorily explained. Some believe its source to be in certain chemical metabolites of the sterol group of substances, but there is more reason to believe that some other endocrine gland, most likely the adrenal cortex, may play an estrogenic role after the menopause.

In any event, the menopausal symptoms are due to the disruption of the previously reciprocal interaction of the pituitary and ovaries. Just how this brings about the symptoms we cannot say. There is increasing evidence of a close liaison between the endocrine system and the higher centers, particularly in the region of the pituitary, though no one can speak with precision as to the pathways involved. The menopausal flushes in many ways resemble physiologically the vasomotor phenomenon of blushing, but just how the endocrine disturbance is translated to the vasomotor apparatus, and why the unpleasant symptoms disappear after a time, even though the endocrine imbalance still apparently persists, no one can say.

The bearing of menopausal hormonology upon the endocrine treatment of climacteric symptoms is obvious. The rationale of estrogenic therapy seems clear, and is now universally accepted. Such treatment substitutes for the lack of the patient's own estrogen, letting her down more gently and gradually in this transition period, and removing temporarily the immediate cause of the symptoms. Even those who are inclined to ascribe the symptoms to the gonadotropic excess rather than to the estrogen deficiency will agree that the best hormonal means of inhibiting excessive gonadotropic function is through the administration of sufficiently large amounts of estrogen, a principle which we utilize in the treatment of various gynecologic functional disorders.

All this may seem at first sight to have moved us in a circle to that day, nearly a half century ago, when ovarian therapy was first begun in the treatment of ovarian deficiency disorders, practiced thereafter with enthusiasm by some and ridiculed by others, until the more accurate knowledge of recent years has unified gynecologists as to the value of the ovarian therapy of today in the treatment of menopausal symptoms. A backward glance over the years fully justifies the hard-boiled skeptics who believed that the ovarian therapy available for the

ment be avoided as far as possible, particularly in women who because of hereditary or other factors might be expected to belong to the cancer-susceptible group.

There is no doubt that the estrogens have often been used in unnecessarily large doses and in an indiscriminating way. When this occurs at the menopause, uterine bleeding may be provoked. This may be a disturbing complication when it occurs many months or even several years after the cessation of the menstrual function, as it raises the possibility of intrauterine adenocarcinoma, and may call for diagnostic curettage to eliminate this possibility. I have recently seen such bleeding in a woman who had been given an average weekly dose of 100,000 international units for several months. Incidentally, the history of this patient led me to believe that there had been no indication for any estrogenic treatment whatsoever.

Finally, no discussion of menopausal therapy would be complete without some mention of the nonhormonal estrogenic substances which for the past two years or so have been employed in an experimental way as substitutes for the natural or synthetic hormones. The chief representative of this group of substances is the stilbene derivative known as stilbestrol. Its chemical structure is not in any way like that of any of the estrogens, and yet it has powerful estrogenic activity, more marked, indeed, than the natural hormone derivatives themselves. While not available commercially, the experimental clinical study of stilbestrol which has been made in many clinics has led to practically unanimous agreement as to its estrogenic potency. Unfortunately, however, it possesses the serious disadvantage of a considerable degree of toxicity, many patients being unable to take it because of nausea, vomiting, vertigo, and other unpleasant symptoms. The incidence of such toxic effects has varied widely in different reports between such extreme limits as 10 per cent and 80 per cent.

Moreover, it is still too early to be sure whether long-continued use of stilbestrol carries with it any more serious danger than the comparatively mild and apparently very temporary toxic effects which have thus far been noted. Work along this line is being pushed, and it seems reasonably certain that sooner or later a simple estrogenic chemical will be evolved which will be free of the toxic properties of stilbestrol. The inexpensiveness of such chemicals as compared to the high cost of hormone preparations will make this a real boon. In the meantime those who employ stilbestrol should be cautious in the matter of dosage, and should be on the alert for symptoms of toxicity. My experience has led me to feel that the daily oral dose in menopausal cases should rarely if ever be over 1 mg.

It would be beyond the limits of a paper of considerate length to include a discussion of certain pathologic manifestations which may be noted at the climacteric, such as (1) involutional melancholia, which gynecologists see far more rarely than do institutional psychiatrists, and which is probably less intimately linked up with the cessation of ovarian function than some would have us believe; (2) the so-called climacteric arthritis, concerning which there is also some question, but which does seem related to this epoch, being characterized most often

preparation in oil is given every third day for from two or three to as many as six or eight injections. Usually the symptoms are so ameliorated after a few injections that the latter may be stopped. In some cases smaller dosage will suffice. The quantitative relationships vary so much in different women that the effective dose must also vary, aside from the varying severity of the symptoms.

In the interval between exacerbations, which have a tendency in many cases to occur at approximately four-weekly intervals, the patient can be kept quite comfortable by one of the oral estrogenic preparations, for estrogen is effective when given by mouth. However, the dosage required for the same effect is many times (estimated variously at from five to a hundred) that necessary for the hypodermic route. It is true that the latter is more disagreeable to the patient, but it is, in my opinion, so much more effective in the severe cases that it is to be preferred. The objection urged by some that the vegetable oil in which the hormone is dissolved often remains to form a painful nodule is not confirmed by my own experience. In mild cases, or in the intervals between severe exacerbations, the oral method would naturally be preferred. It is clear, therefore, that even in those women who suffer a severe and prolonged menopause, constant hypodermic medication is not required, and by a combination of the hypodermic and the oral routes almost all patients can be kept reasonably comfortable. Again, it should be emphasized that active endocrine therapy of this sort is necessary in only a small proportion of menopausal women. The great majority of women at this epoch require no treatment at all, or only such simple measures as reassurance and perhaps the employment from time to time of simple nerve sedatives, such as the barbiturates.

The question is often asked as to whether or not the prolonged use of estrogens can produce harmful results, especially in predisposing to the development of cancer. The relation between estrogenic and carcinogenic substances has been in the forefront of discussion for several years, and the question is too big a one to elaborate in this paper. Suffice it to say that there is as yet no worthwhile evidence to indicate that even large therapeutic doses of estrogen, far larger than are necessary in menopausal cases, carry with them any risk of inciting cancer. The experimental production of cancer in certain animals by means of estrogen injection has been possible only through the prolonged use of huge doses, many times as large as would ever be justified therapeutically, and in animals of a cancer-susceptible strain.

Granting all this, however, we must remember that certain human beings are quite certainly also unusually cancer susceptible, so that, even in the absence of convincing direct evidence on this point, the theoretical possibility of exciting such a latent tendency through excessive estrogenic therapy cannot be excluded. In the present state of the question, there is certainly no justification for withholding proper estrogenic therapy when menopausal symptoms are troublesome, with the reservation that excessive or unusually prolonged treat-

PREGNANCY AND DISEASE

HUGO EHRENFEST, M.D., ST. LOUIS, MO.

WITHIN the last two decades a great deal of new information has become available in regard to certain biochemic and functional alterations typically occurring all through the maternal organism under the influence of a normal pregnancy. Careful study and judicious interpretation of all these manifold changes justify the conclusion that they serve a rational purpose and in the last analysis accrue to the benefit of the fetus in utero. The fact that identical, or at least very similar, alterations to a limited degree are also found in the premenstrual phase must be accepted practically as proof for the modern conception of menstrual function as periodic, local, and systemic preparation of woman for a pregnancy. Indeed, the premenstrual structural modifications of the endometrium are now customarily designated as "progestational" or "pregravid."

With the onset of pregnancy, that is with the realization of the merely anticipated implantation of a fertilized ovum, these characteristic, local and systemic premenstrual changes not only persist but immediately become intensified. We may well say that while the premenstrual changes solely express *qualitative* requirements, they adapt themselves with the onset of pregnancy to actual *quantitative* needs. This biologic adjustment of the entire body occurs in response to specific stimulation by definite hormones, which during pregnancy, as we at present believe, are chiefly elaborated by chorionic tissue.

Normal physiologic pregnancy reactions in general imply an increase both in functional ability and functional activity of various organs and organ systems. As a whole, this effect proves advantageous and usually results in some permanent benefit. Clinical experience shows that, as a rule, a woman at the start of her second pregnancy proves biologically better equipped for gestation.

Reproduction represents the maximum of physiologic ability of woman and therefore necessarily calls for maximal functional activity of practically all her organs. While admittedly lying within the limits of physiologic normality, the morphologic, chemic, functional, static, and emotional alterations brought on by pregnancy often will give rise to clinical manifestations which in a nonpregnant individual always would indicate a truly pathologic condition.

The feeling of well-being is determined by an harmonious interaction of all organic functions under control of the autonomic nervous system. This equilibrium is likely to become disturbed, at least temporarily, at the onset of pregnancy, if with the sudden call for greatly increased activity some of the important vital organs fail to respond promptly or adequately. The molimina of early pregnancy, with relatively rare exceptions, subside or disappear completely within the first twelve weeks. The disturbed equilibrium evidently has been restored.

by pain and swelling of the knees, with often rather typical supra-condyloid tenderness; (3) the moderate climacteric hypertension, often of fluctuating type, which many have noted at, and just after, the menopause, and which is likely to be transient and apparently favorably influenced by estrogenic therapy; (4) functional uterine bleeding, an exceedingly common but easily curable gynecologic disorder of this life period.

SUMMARY

In spite of a healthier attitude among women in general as to the significance of the menopause, there is still a considerable substratum of misconceptions on this point, and the physician must take cognizance of this in the management of climacteric women. The majority of women at this phase need no treatment at all, many require only reassurance and education, and in only a comparatively small proportion is ovarian endocrine therapy necessary. There is perhaps no gynecologic disorder in which the indication for organotherapy is more rational than in the treatment of typical climacteric symptoms, especially the vasomotor group. There is a definite field for both the parenteral and oral routes of administration of the estrogenic hormones, the former being much more effective when the symptoms are severe.

On the other hand, it must be remembered that many symptoms frequently observed in menopausal women are not directly due to the endocrine readjustments of this period, but that they are more logically explained as due to environmental and psychogenic factors of one sort or another. The physician who depends upon endocrine therapy alone will fall short of the requirements in many cases, and indiscriminate estrogenic therapy should certainly be frowned upon.

The question of the possible hazard of inciting malignancy in cancer-susceptible individuals cannot be decided too arbitrarily in the present state of our knowledge, though it is fair to state that no impressive evidence of such a danger has as yet been adduced, after many years of employment of the method. Certainly it would at the present time be carrying conservatism and caution to an extreme to deprive the menopausal woman of proper estrogen therapy when this is otherwise indicated, merely on the basis of this slight theoretical possibility.

Stilbestrol, because of its high degree of estrogenic activity, is very effective in the control of menopausal symptoms, but its use carries with it the disadvantage of toxicity in a considerable proportion of cases, in my own experience about 20 per cent. While these are practically always mild and while they disappear with cessation of the drug, their occurrence makes it inadvisable to release the preparation for general clinical use, especially in view of the uncertainty as to the possible effects of its long-continued use. The dosage should be kept at the lowest effective level, and it is only rarely necessary to employ more than 1 mg. daily.

In the cases falling into the two last mentioned groups, both frequency and intensity of effects on either pregnancy or disease are chiefly determined by the nature of the disease. A detailed discussion of all these possibilities, of course, becomes impossible within the limits of this mere survey. However, it is possible to discern basic causes for untoward effects of pregnancy and disease on each other which are common to many of the diseases most often encountered in obstetric practice.

A. EFFECTS OF MATERNAL DISEASE ON PREGNANCY

1. A fairly frequent consequence is premature expulsion of the uterine contents as a result of primary fetal death. The fetus may fail to obtain a sufficient supply of oxygen (e.g., in advanced pulmonary diseases, chronic or acute; cardiac failure, etc.), or to receive certain nutritive materials in required amounts (marked general debility or exhaustion from various causes). Since the intrauterine temperature is higher than that of the mother, in cases of high fever (especially with sudden rise following chills), the fetus may actually succumb to a heat stroke. Some maternal diseases are transmitted to the fetus by way of the placenta. Viruses and bacterial toxins (smallpox, typhoid, etc.) can pass through the intact placenta. In diseases caused by micro-organisms (syphilis, tuberculosis, malaria, etc.) their transition to the fetus is usually made possible by degenerative processes in the placenta which destroy the normal chorion-epithelial barrier against passage of form elements between maternal and fetal blood. Certain poisonous substances (such as lead, morphine, nicotine) will filter gradually, or suddenly in large amounts, into the fetal blood stream.

2. Premature uterine activity in some instances is due to abnormally increased general nervous irritability. Strong uterine contractions, initiating an abortion or premature labor, are not infrequently observed in connection with excessive intestinal peristalsis brought on by intestinal disease or strong cathartics. Premature uterine activity may follow administration of certain drugs; e.g., ergot or quinine. It must be emphasized, however, that quinine is given in all cases of malaria, because more fetal lives thus are saved through the prevention of further chills.

3. In general, the resistance of the fetus against all unfavorable influences of a concomitant maternal disease increases as pregnancy advances. Therefore, in the later stages of gestation, transition of micro-organisms, viruses, or bacterial toxins (possibly simultaneously with immunizing antibodies) will not necessarily lead to fetal death. Under such conditions, particularly in cases of acute infectious diseases, the liveborn infant can show evidences of the transmitted disease in an active stage (syphilis, smallpox, tuberculosis, occasionally also malaria) or exhibit the proof of recovery from the transmitted disease in form of typical scars (smallpox), or by failing to react to specific vaccination (smallpox) or by yielding (typhoid) a positive Widal reaction. A positive Wassermann reaction will establish the latent stage of transmitted syphilis.

In the constitutionally normal and healthy woman, the adequate adjustment to greatly augmented functional demands is facilitated by the fact that in a normal individual all the organs participating in vital functions evidently are endowed with a physiologic reserve available for emergency.

This important reserve endowment, however, will be limited or entirely absent in women who may be classified as constitutionally deficient. In some of them, certain organs or organ functions may not have fully developed through premature arrest in normal postfetal development; in others, they may have become damaged by disease, often during childhood. In such individuals the actually present functional limitations frequently remain unnoticed under a normal mode of life. They manifest themselves only with the onset of a pregnancy, and then response to increased demands is slow or insufficient. Under the strain of enforced overactivity, which increases as pregnancy advances, in such primarily only functionally deficient organs, morphologic changes of a definitely pathologic nature are likely to develop. Signs of seemingly only transient inadequacy may thus during pregnancy change, often imperceptibly and unexpectedly, into symptoms of actual disease.

Pregnancy by itself must undeniably be accepted as a possible direct factor in the origin of disease; however, with improved antenatal technique and newer methods of dealing with severer disturbances of pregnancy, the belief in the importance of reproduction as a frequent or basic cause of disease has diminished to a noticeable degree. It has become apparent that a medical, mental, and occasionally even a surgical disease, which manifests itself during or soon after pregnancy, more commonly represents the recurrence or acute exacerbation of a pre-existing pathologic condition which had remained latent under the conditions of a normal life.

At the first antenatal examination, made as early as possible, the patient must be questioned in regard to all previous medical, surgical, or mental diseases and symptoms. At this occasion a careful physical examination, which now almost routinely includes a Wassermann or Kahn test, should attempt to ascertain the presence or absence of any maternal disease. There can be noticed an increasing tendency to subject all suspicious cases to a tuberculin test or x-ray study of the chest. Oral examination and inquiry into food habits have become routine with growing appreciation of dental caries and deficiencies in mineral and vitamin intake in the causation of various complications of pregnancy.

Comparatively few diseases preclude the possibility of impregnation, and therefore practically every known disease at some time has been encountered in a pregnant woman.

Such an association of pregnancy with disease can express itself in three possible forms: (1) Disease and pregnancy independently follow their usual course. (2) The coexisting maternal disease affects pregnancy, labor, puerperium, and possibly also the future health of the liveborn infant. (3) An intercurrent impregnation aggravates, but occasionally even improves, the usual course of the associated disease.

loss, general debility, and shock. Fortunately all these risks can now be greatly reduced, if not fully eliminated, by appropriate obstetric procedures.

The foregoing theoretical considerations of the manifold interrelations between pregnancy and disease can leave no doubt in regard to the significance of prompt diagnosis of a disease accompanying pregnancy. In case of any doubt concerning exact diagnosis and appropriate treatment, the obstetrician, therefore, has learned to appreciate aid from the respective specialist. Most of the larger obstetric services in this country at present include in their regular staffs experts in diseases of the heart, lungs, and kidneys. Incidentally the fact may be emphasized that this cooperation of obstetricians with other specialists in prenatal care has resulted in our present, greatly advanced information concerning the complex interactions between pregnancy and disease.

In this problem there arise still other weighty questions which the attending physician or obstetrician has to answer. Not so rarely he is called upon to make vital decisions in regard to such other closely related problems as *advice against marriage*, *prevention of pregnancy*, or *interruption of pregnancy*. Obviously the answer in each instance will depend chiefly on the nature and state of the particular disease. Nevertheless it is possible to group at least some basic principles for decision which apply to several of the more common diseases.

1. *Advice Against Marriage*.—In some states of this country premarital certification of absence of venereal disease, especially of syphilis, now is legally required. Wider diffusion of present knowledge in the problems of heredity and eugenics plausibly accounts for a noticeable increase in voluntary premarital medical consultations.

Marriage often promises for the woman an improvement in her social-economic condition, which may enable her to nourish herself better, to work less, and even to secure more efficient treatment of her disease.

A strong warning against marriage will always be justified if the woman is suffering from a disease which can be expected to be greatly aggravated by pregnancy; if either man or woman, contemplating marriage, is suffering from a medical, surgical, or mental disease which is prone to lead soon to physical incapacity or death; and if either party has a disease which could, or usually is, transmitted to the offspring, or is likely to disturb or prevent satisfactory and harmonious union in marriage.

2. *Prevention of Pregnancy*.—Obviously, marriage does not necessarily imply the occurrence of pregnancy and thus the possible risks connected with it. The chances of impregnation can be greatly reduced by intelligent and faithful use of some of the methods of contraception now available. They prove particularly useful when prevention of impregnation is desirable or necessary for only a limited period of time. In this respect, under prevailing conditions, the physician also must take into account the social-economic status of the patient. One more pregnancy may not necessarily aggravate seriously the associated disease (a quiescent pulmonary tuberculosis or a compensated heart

4. Acute infectious and contagious diseases (scarlatina, erysipelas, diphtheria, etc.) are prone to cause serious complications of the puerperal state.

B. EFFECTS OF PREGNANCY ON A COEXISTING MATERNAL DISEASE

Mention already has been made of the important fact that both the disease and the pregnancy can, without any noteworthy influence on each other, run their usual courses. As far as such lack of effect on an associated disease is concerned, it holds true for the great majority of cases seen by the obstetrician.

The heretofore widely prevailing belief in inevitable and dangerous consequences of an intercurrent pregnancy on some diseases (especially pulmonary tuberculosis and cardiac disease) is steadily weakening, parallel with an ever increasing conviction that the fate of the sick and pregnant woman is actually determined by proper and adequate treatment of her disease. The present tendency to install maternity departments in all larger tuberculosis sanatoriums is one of the most striking evidences of newer conceptions in regard to appropriate dealing with the disease in a pregnant woman.

Pregnancy and labor are likely to supply some factors which may adversely affect the course of certain maternal diseases. The most common and more important of these factors can be grouped as follows:

1. Exaggerated vomiting may increase the patient's debility and thus lower resistance to the associated disease. Marked malnutrition, starvation, vitamin deficiencies, etc., will aggravate or actually initiate various pathologic conditions.

2. Physiologic, gradually increasing and enforced overactivity of already diseased organs is likely to lead to serious morphologic deterioration with proportionate decrease or almost complete annihilation of their functional abilities. Such consequences occur most often and most markedly in connection with diseases of the kidneys, liver, heart, and lungs. As far as functional anomalies of thyroid or pancreas are concerned, the stimulating effect of an intervening pregnancy or fetal demands, in some instances, may actually improve the patient's condition.

3. Particularly, in the advanced stages of gestation, the large uterine tumor exerts pressure against various abdominal viscera. The possible results are: Reduced amplitude of respiratory movements of the diaphragm, interference with intestinal peristalsis, with passage of urine from kidney to bladder, or with blood circulation. It is obvious that in this manner the course of diseases of the respiratory, gastrointestinal, urinary, or circulatory systems can be adversely affected. This same mechanical effect, however, may prove beneficial, e.g., in a case of marked nephroptosis. It has been claimed by some authorities that the steadying effect of the large uterine tumor on the diaphragm in some respects resembles the beneficiary effect of artificial pneumothorax or phrenicectomy in cases of acute pulmonary tuberculosis.

4. Among unfavorable influences connected with labor, delivery, and lactation, the most common are: Severe pain, physical exertion, blood

ally represents a very serious complication. However, the obstetrician now is less intimidated by the presence of a maternal disease, is less inclined to proceed forthwith with termination of the pregnancy, and exhibits much more interest in the coincident disease.

It is regrettable but probably inevitable that in spite of extensive and careful studies no reliable information, not even in regard to such more common diseases as tuberculosis, nephritis, or cardiac lesions, is available concerning their incidence among pregnant women, their consequences both for mother and fetus, and the best forms of medical and obstetric management. Wide variations and actual contradictions can be noticed in data and conclusions offered by large obstetric services of this and foreign countries. As a matter of fact such statistics are not comparable. The clinic equipped with a staff of experts in various special fields necessarily will show a surprisingly high incidence of associated diseases. The inclusion, in large numbers, of cases discovered in a very early stage is bound to vitiate statistical deductions, e.g., in regard to results obtained with this or that favored method of treatment. This same therapeutic procedure may statistically have proved entirely inadequate in another maternity service which, possibly for solely local reasons, is admitting in an unduly large proportion rather advanced cases of a certain type of disease.

In the individual case the attending obstetrician remains the final judge, but it can be assumed that familiarity with certain basic principles outlined in the foregoing pages will prove helpful to him in making his decision.

lesion), but one more child may well imply hazardous reduction in required rest or even food supply.

Reliable and continuous prevention of pregnancy is clearly indicated, e.g., in advanced cases of tuberculosis, nephritis, cardiac lesions, in instances of associated malignancy and certain forms of mental disease. Permanent sterilization is secured only by operative procedures either on the wife or the husband, which during the last two decades have been almost standardized.

3. *Interruption of Pregnancy.*—Deliberate termination of a pregnancy always is a hazardous operation, and its risks are inordinately increased when done on a seriously sick woman.

Relatively few pathologic conditions still are accepted as definite indications for interruption of pregnancy: laryngeal tuberculosis, otosclerosis, certain forms of insanity. In the majority of instances a decision for termination of pregnancy becomes justified because in spite of appropriate therapy the patient's disease shows evidence of further aggravation.

As emphasized before, prompt and adequate treatment of the associated disease today is generally recognized as the best means of safeguarding the mother, and for this reason the incidence of so-called "therapeutic" or "medicinal" abortions is continuously decreasing, at least in all large obstetric services.

While interruption before viability necessarily means the deliberate sacrifice of the fetus in the interest of the mother, the situation is entirely different when termination of gestation is taken under consideration after fetal development has reached a stage where extrauterine continuation of his life is possible or probable. Under these circumstances premature start of labor may become justified as well in the interest of the child. However, when thus considering and weighing the best interests, both of mother and infant, the most difficult problem for the obstetrician occasionally arises in the decision whether the patient's condition safely permits continuation of gestation until fetal viability is reached. Here again the value of advice from a specialist is obvious.

In this connection a few remarks must be made in regard to cesarean section. Under certain conditions this operation undeniably offers the best chances for both the sick mother and the child. It eliminates several of the special risks of labor and delivery and incidentally offers a ready opportunity of securing permanent sterilization which may be indicated by the complicating disease. However, this latter advantage does not warrant the growing tendency toward performing a cesarean section at or near term simply because sterilization is justified in the particular case.

In concluding this survey I can assert that within the last twenty years our knowledge of the possible influence of pregnancy and disease on each other has been greatly enriched, though it remains wanting in many respects. In medical writings the formerly customary term "pregnancy complicated by disease" is being gradually replaced by the more optimistic phrase "pregnancy associated with disease," which, of course, does not deny the possibility that such association occasion-

A. IMMEDIATE DANGERS

1. *Hemorrhage*.—From the earliest days of cesarean section, hemorrhage was one of the two most serious complications, the other being sepsis in the form of peritonitis. During the last twenty years hemorrhage has been so minimized, it is no longer the dreaded complication of former days. Improvement has come through the proper suturing of the uterine wound, the use of posterior pituitary extract injected intravenously if the condition so warranted, and the use of ergonovin, which will prolong the contraction of the uterus. Ether narcosis, which is responsible for relaxation of the uterus during operation, often has been supplanted by local infiltration anesthesia and by the various gaseous mixtures which have come into use during recent years. Blood transfusion, which was more of an innovation than the cesarean section itself twenty years ago, has been so simplified that it is now administered to the patient in her own bed, and, because of this, blood loss is easily replaced. The cervical or lower segment of the uterus when incised is much less likely to bleed than the corpus or upper segment. The performance of hysterectomy for uncontrollable hemorrhage following cesarean section has become a rarity at the present time.

2. *Trauma of Operation*.—Improved technique, gentle handling of the tissues, and conservation of blood have markedly decreased shock following abdominal delivery. It is conspicuously absent after the low or cervical cesarean section. It is more commonly observed in the cases of gravidocardiacs, but even in this group of cases it has been reduced to almost negligible proportions by operating under local infiltration anesthesia.

3. *Sepsis*.—Even more than hemorrhage, infection has been and still is the most important factor in mortality and morbidity in cesarean section. It stands out today as the most severe complication of the operation.

The contributing factors to infection in cesarean section are long labor, rupture of the membranes, repeated vaginal examinations, and the state of exhaustion and lowered resistance in which the mother has been placed after a protracted labor.

Protection against sepsis may be obtained by early interference when abdominal delivery is indicated and by the proper selection of the operative procedure. The work of Harris and Brown, carried out during the period of time in which we are reviewing the progress of cesarean section, has shown that bacterial invasion of the uterus occurred early in labor, even with unruptured membranes. The classical cesarean section offers no protection against peritoneal contamination at the time of intervention or thereafter. In view of the above cited work, this operation may be considered relatively safe before labor or at most at the onset of labor, but it becomes unsafe after labor has been established a number of hours, even though the membranes are still intact.

The low or cervical operations have considerably decreased the infections, although they have not absolutely controlled them. The progress of the last two decades has been in the saving of maternal lives

THE PROGRESS OF CESAREAN SECTION

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

THE last twenty years form an important milestone in the development of cesarean section. Previous to 1920, the Säger or classical cesarean section was usually resorted to and the lower segment operation was but seldom employed. It is during the last two decades that numerous modifications in technique have been elaborated to increase the safety of the latter procedure. A review of the forty volumes of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, from 1920 to 1940, paints a clear picture of the evolution of the low or cervical cesarean sections. Two considerations of cesarean section stand out:

First, The Living Child.—From the earliest times the first consideration of cesarean section has been the living child. In the earlier days speed of operating was presumed to be important, for it was thought that the sooner the child was born, the greater were its chances of surviving this method of delivery. With speed in mind it was not uncommon to see the abdomen and uterus opened with one sweep of the knife. Naturally, accidents resulted, such as injuring or cutting the intestine which had found its way in front of the uterus; the placenta was incised if inserted on the anterior surface of the uterus, this being accompanied by free hemorrhage. Furthermore, babies were injured by the too deep penetration of the knife in the uterine musculature.

Improvement in operating in general, as well as other factors, has shown that time is not the only *element* which enters into a successful operation. Due thought to the duration of anesthesia during a forceps delivery might have brought to mind that undue emphasis was placed on the necessity of shortening the time of anesthesia. Other conditions affecting the child's welfare during the performance of cesarean section are the administration of morphine too soon before starting the operation, thereby resulting in intrauterine asphyxia; trauma to the child by attempting delivery through an inadequately long incision; and disturbance in the child's nutrition in the presence of ablatio placentae and placenta previa. In recent times it has definitely been shown that prolonged anesthesia in the too slow extraction of the child is rarely a factor in the hands of competent operators.

Second, The Welfare of the Mother.—When it was realized that a living baby could be easily obtained, and that the earlier techniques often resulted in complications which were serious, if not fatal, to the mother, due consideration was given to her welfare.

The dangers or disabilities to which the mother is subjected when a child is delivered abdominally may be classified as immediate or late dangers.

that in the performance of cesarean section the lower uterine segment may be approached in one of three ways: (1) intraperitoneally; (2) transperitoneally (peritoneal exclusion); and (3) extraperitoneally. In each instance the lower segment may be opened by a longitudinal or vertical incision, or by a transverse incision.

1. *Intraperitoneal Cervical Cesarean Section*.—This is referred to as the Kroenig-Beck-DeLee, and low flap operation. Essentially it consists of a vertical abdominal incision, a transverse incision in the visceral peritoneum, separation of the bladder with a lower flap of peritoneum, the dissection of an upper flap of peritoneum if one prefers, and a vertical incision in the lower segment. After delivery, the cervical incision is closed and the peritoneal flaps overlapped, sealing the uterine incision from the general peritoneal cavity.

In 1926 I proposed the transverse incision placed entirely in the lower segment after free separation of the bladder, with the main idea of preventing extension of the incision in the musculature of the uterine corpus when the lower segment was not well formed, or when delivering a large fetus. Munro Kerr had advocated a similar transverse incision which he placed at the isthmus or junction of the corpus and cervix without mobilizing the bladder.

2. *Transperitoneal Cervical Cesarean Section (Peritoneal Exclusion)*.—This operation is known as the Veit-Fromme-Hirst procedure. Veit and Fromme of Halle, in 1908, proposed a method whereby an extraperitoneal space for delivery was created by uniting the layers of the dissected visceral peritoneum to the parietal peritoneum by means of sutures or clamps, to protect the peritoneal cavity from the spill, and to leave the uterine incision outside of the general peritoneal cavity during the process of healing. Barton Cooke Hirst of Philadelphia, working independently, offered a similar procedure. More recently E. F. Smith of New York submitted a technique of peritoneal exclusion through a Pfannenstiel incision, and with a transverse incision in the lower segment in order to overcome one of the disadvantages of the Veit-Fromme-Hirst, namely the fixation of the lower uterine segment to the abdominal wall. Smith's operation is a modification of Sellheim's third method proposed in 1908. Peritoneal exclusion is recommended for the woman who has been long in labor, with or without ruptured membranes, but with potential infection. That the procedure recommended by Smith protects such a patient against peritonitis was forcibly brought to my attention in the case of a young woman on whom I performed this operation, after she had been in labor nearly forty-eight hours, and when she showed signs of exhaustion and early infection. She had a febrile puerperium and septic endometritis, her temperature reaching 105° F. for a number of days. She was discharged from the hospital at the end of two and one-half weeks, and examination two months later showed the uterus to be well involuted, in forward position, freely movable, and the pelvic organs in normal condition. Although she ran this septic course there were no signs of peritonitis.

3. *Extraperitoneal Cesarean Section*.—The extraperitoneal cesarean section is represented by the operation of Latzko. Advantage is taken

of those in whom abdominal delivery was imperative, by the application of the extraperitoneal technique and its modalities. Mayes, of Brooklyn, and Brown, of St. Louis, have shown by careful bacterial and clinical studies that infection at cesarean section could be decreased by the instillation of antiseptics in the vaginal tube before operation. The former advocated mercurochrome and the latter neutral acriflavine. In a small number of cases of our own, we have found their contentions to be true. Thus, antisepsis has been added to asepsis.

B. LATE DANGERS OR DISABILITIES

1. *Invalidism*.—Following a major surgical operation, a number of women may have poor health for a more or less prolonged period of time. This is especially true if the operation has been associated with sepsis and hemorrhage. The period of recovery from operation varies with the patient's general condition at the time of intervention and with the presence or absence of postoperative complications.

2. *Sterility*.—In marked infection with suppuration following cesarean section, there may be partial or, in the severe cases, complete destruction of the endometrium, sometimes resulting in sterility. Two such patients have come to our observation. In one, there had been prolonged uterine suppuration following a peritoneal exclusion operation, and in the other, extreme sepsis following the Gottschalk-Portes exteriorization of the uterus. In both, the endometrium completely sloughed off, and these patients have never menstruated since. In the lesser degrees of sepsis, while amenorrhea may not result, there may be enough endometrial disturbance to cause sterility.

3. *Rupture of the Uterus*.—Imperfect healing of the uterine incision with subsequent rupture in following pregnancies and labors is to be thought of when cesarean section is contemplated. Statistics show this to occur in about 3 per cent of the classical cesarean section cases, and less than 1 per cent in the low or cervical operations. This is another respect in which the low operation has increased the safety of abdominal delivery.

The six factors mentioned above have been influential in the development of the technique and of the progress made in the performance of cesarean section in the last two decades.

PROGRESS IN TECHNIQUE

Before 1920, Beck, DeLee, Polak, and myself were strong advocates of the newer method of performing cesarean section. At that time the classical operation was the method universally used in America. During the twenty years which followed, the low or cervical cesarean section, to which DeLee has applied the term *Laparotrachelotomy*, has gradually supplanted the older operation in a number of important clinics, and DeLee, more than any other, must be given the credit of popularizing this intervention by his constant emphasis upon its superior merits. During the period of review, minor modifications in technique have been added by numerous operators. The important principles rest upon the fact

The chief contraindications to cesarean section are (1) a dead child, except in the presence of an absolute pelvic indication; (2) poor physical condition of the mother; (3) improper surroundings for aseptic technique; (4) a patient infected from protracted labor, vaginal examinations performed with questionable antisepsis and asepsis, and rupture of the membranes; (5) the classical cesarean section is absolutely contraindicated in the presence of a potential or frank infection.

The newer methods of performing cesarean section, largely standardized during the last two decades, will doubtless continue to play an important role in reducing morbidity and mortality. Finally, careful prenatal study, the use of x-ray pelvimetry, recently developed, examination before labor, under anesthesia if necessary, a test of labor under aseptic conditions, followed by the low or cervical operation when indicated, the use of vaginal antiseptics added to a rigid aseptic technique, and limiting the operation to strict indications will all help in keeping morbidity and mortality in cesarean section at the lowest possible figure.

REFERENCES

- Phaneuf, L. E.*: Surg. Gynec. Obst. 47: 851, 1928. *Waters, E. G.*: AM. J. OBST. & GYNEC. 39: 423, 1940. *Smith, E. F.*: Ibid. 39: 763, 1940.

270 COMMONWEALTH AVENUE

of the loosening and raising of the peritoneal sac from the lower uterine segment after a long labor. This procedure is performed through a vertical abdominal incision, the intact peritoneal sac is raised upward from the bladder and the bladder is displaced laterally to the right. This clears a space in the lower segment which is ample for the placing of a longitudinal or vertical incision of sufficient length for delivery. This method, reserved for potentially or frankly infected women, has replaced the radical or Porro cesarean section in a number of clinics. Its technique is more difficult than that of the intraperitoneal and transperitoneal operations, but in the hands of a trained pelvic surgeon, the difficulties are far from being insurmountable.

Edward G. Waters of Jersey City, New Jersey, during the present year, has published on the supravescical extraperitoneal cesarean section a true extraperitoneal operation simpler in performance than is the Latzko. In his method Waters has substituted a transverse incision for the longitudinal incision of the lower segment as used by Latzko. The operation of Waters will no doubt prove to be the most popular as it is taken up throughout the country.

Vaginal cesarean section, devised by Dührssen, for the rapid emptying of the uterus before term, and also to overcome the disadvantages of accouchement forcé, was used during the days when it was felt that the uterus should be emptied immediately for eclampsia. During the last twenty years the treatment of this disorder has been along conservative lines, treating the toxemia and disregarding the pregnancy for the time being. As a result of this the vaginal cesarean section has practically disappeared from the obstetricians' armamentarium.

Gottschalk-Portes operation, or temporary exteriorization of the uterus, has rendered important service in the exhausted, badly infected patient. Its employment will always be necessarily limited. I have saved two maternal lives and one fetal life by resorting to this procedure, when it was felt that all other methods would have failed.

COMMENT

A careful consideration of the progress of cesarean section from 1920 to 1940 has shown us that this operation is not a panacea for all obstetric ills. The indications, which doubtless were extended because of the increased safety of the low or cervical operations, should be carefully evaluated and should be reduced to a minimum. While the general surgeon, technically, may perform a perfectly adequate operation, his training is not such that he may evaluate the purely obstetric methods against abdominal delivery in a given case. In such instances, the requirement of a consultation with an obstetric consultant, as is done in a large number of hospitals, will have a salutary effect in reducing morbidity and mortality. The improved results of cesarean section in the hands of the trained obstetric specialist may not be due to the fact that he can perform the operation better than the general surgeon, but rather because of the fact that his obstetric training has taught him the contraindications to this operation, which he observes.

also claimed that there is a third, an "interstitial-cell-stimulating" hormone. The final answer to this problem awaits the chemical identification of the active pituitary substance or substances concerned with these changes.*

With the exception of glands obtained from pregnant women, the anterior hypophyses of men and women, at all ages from fetal life to senility, have strong gonadotropic properties. In addition, anterior pituitary gonadotropin may be demonstrated in the blood and urine by means of the Aschheim-Zondek test under certain circumstances. For instance, its concentration increases at about the time of ovulation during the normal menstrual cycle, and large amounts are observed following castration or the menopause. These findings indicate that the ovaries also act on the anterior lobe and inhibit the production of its gonadotropin, a fact which is recognized in attempts to explain the mechanism of the menstrual cycle.

In 1928, it was announced that a potent gonadotropic substance occurs in the urine of pregnant women, and its demonstration is now widely employed as a "pregnancy test." At first it was believed that this hormone is produced by the anterior hypophysis, but evidence is accumulating showing that it is elaborated by the placenta. There are many biologic differences between the two gonadotropins. For instance, in hypophysectomized rats anterior lobe extracts stimulate the growth of follicles and the development of corpora lutea, while the injection of preparations of urine from pregnant women merely results in a hypertrophy and hyperplasia of the interstitial tissue. It also has been shown that a gonadotropin is formed in cultures of placental cells. The hormone found in pregnant women is now known as the "chorionic gonadotropic hormone"; but as in the case of the other gonadotropins, its chemical structure has not been determined. In addition to the placenta, it is also produced by cellular constituents of hydatidiform mole, chorionepithelioma, and certain tumors of the testes.

Ten years ago another gonadotropic factor, having certain biologic properties common to both the anterior pituitary and chorionic hormones, was discovered in the blood of pregnant mares. This remarkable substance is exceedingly potent in stimulating the gonads of many species. It occurs in the blood of mares during the middle third of the period of gestation, and is excreted only in small amounts, if at all, in the urine. This equine hormone may in time become an important therapeutic agent.

LACTOGENIC HORMONE

Among the many functions attributed to the anterior hypophysis, the fact that it stimulates lactation is of special interest to obstetricians. Although many experiments with crude anterior lobe preparations resulted in changes in the mammary glands, now it is known that they are due, not to a general reaction involving many glands, but to *prolactin*, a specific product of the hypophysis. This substance, in ad-

*Since this article was written the chemical purification of the "luteinizing" hormone from anterior lobe tissue has been announced. It is a protein and also is identical with the so-called "interstitial-cell-stimulating" hormone.

TWENTY YEARS OF PROGRESS IN ENDOCRINE STUDIES OF REPRODUCTION

C. F. FLUHMANN, M.D., SAN FRANCISCO, CALIF.

AMONG the many achievements of medicine of the past two decades, the advances in our knowledge of the endocrine glands must rank as one of the brightest chapters. Of primary interest in this field have been the numerous studies dealing with reproduction, and they have led to discoveries which have clarified many phases of sexual physiology and pathology and also yielded active substances of inestimable value in the therapy of many obstetric and gynecologic diseases.

In the early twenties, a few pioneers struggled with various aspects of these problems, but the forties see a veritable army of investigators and the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY has become an important medium for reporting the results of their work. Evans and Cowles note that during the year 1939 a total of 2,807 papers of endocrine interest were published in 221 journals, and that 34 per cent of this number appeared in eight publications. It is noteworthy that the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY ranked sixth in this group, with a total of 66 contributions.

In the short space available for this review it is impossible to give a complete analysis of the progress made during the last twenty years in endocrine research dealing with reproduction. Nevertheless, on this anniversary of the JOURNAL it is of some interest to note a few of the fundamental discoveries which have been made during its lifetime.

GONADOTROPIC HORMONES

On the basis of clinical observations and of early experiments on hypophysectomized dogs, the existence of a pituitary-gonadal interrelationship long has been recognized; but our present knowledge of the gonadotropic hormones may be said to have originated in 1921, when it was shown that clear-cut changes in the ovaries of rats follow the prolonged administration of suitable extracts of anterior lobe tissue. Since then corroboration has been advanced by many experiments with extracts or implants of fresh material in immature and mature hypophysectomized and intact animals.

As it does with so many other endocrine functions, the anterior lobe of the hypophysis controls the activities of the ovaries. It is responsible for the development of the primary follicles into mature Graafian follicles, ovulation, corpus luteum formation, and indirectly also for the production of ovarian hormones which in turn act on the accessory genital organs. These effects may be readily induced in immature or hypophysectomized rodents, but the question as to whether they are due to one or more hormones is not completely answered. There is strong evidence at present that two factors are concerned, one, a "follicle-stimulating" hormone, and second, a "luteinizing" hormone. It is

menstrual cycle, the concentration of estrogens in the blood and urine varies, a peak usually being found at about the time of ovulation.

A truly magnificent contribution to this field was the chemical isolation of many estrogenic substances, accomplished in an unbelievably short time by several groups of investigators, working in friendly rivalry and yet each adding invaluable assistance. The estrogens which occur naturally in the human being are sterols, and to this group also belong cholesterol, the bile acids, ergosterol, calciferol, and androgenic substances. Three important principles have been isolated from urine and ovarian tissue. The first one recognized was *estrone* and given the formula $C_{18}H_{22}O_2$. A second crystalline substance was then isolated, named *estriol*, with the formula $C_{18}H_{24}O_3$. Finally, *estradiol*, $C_{18}H_{24}O_2$, was extracted from ovarian tissue and recently also from urine. The fact that these compounds are very closely related chemically, and one may be converted into the other, may prove of vital importance in determining the mechanism concerned with the metabolic processes of the physiology of reproduction. An interesting new field of investigation is the quantitative interrelationship of these estrogens during normal gestation and in the course of certain toxemias of pregnancy.

Additional studies of the chemistry of estrogenic hormones have led to many discoveries, one of them being that these active substances may be prepared synthetically. This opens up a field of considerable importance, not only in the study of endocrine physiology, but also in a practical manner, since it will enable commercial concerns to manufacture reliable products for therapeutic usage at much less cost.

PROGESTERONE

In the early years of this century, a number of experimental studies led to the realization that the corpus luteum is a gland of internal secretion. There was much obscurity, however, regarding its exact function, and only in recent years has this been clarified. It is now known that, unlike the estrogens, the hormone of the yellow body is a *specific* substance produced by the ovary. An accurate biologic test for its demonstration has been developed, many aspects of its physiologic activity have been investigated, and it has been isolated as a pure chemical compound.

The hormone of the corpus luteum has been named *progesterone* and its effects, naturally, are apparent when this structure has reached a complete stage of development. The most striking are the progestational changes which it induces. They are seen in the production of "pseudopregnancy" in certain mammals and the characteristic "post-ovulatory" or "secretory" stage of the endometrium of women and monkeys. Thus, it prepares and sensitizes the uterine mucosa for the nidation of the fertilized ovum. When the hormone is administered for a prolonged period, it prevents the onset of menstruation, and it also inhibits the normal rhythmic contractility of the myometrium.

Progesterone is chemically closely related to the estrogens and androgens, and has the formula $C_{21}H_{30}O_2$. It exists in two different

dition to stimulating lactation in mammals and crop-milk formation in pigeons, also can depress the activity of the gonads, and it is an important factor in the development of brooding and maternal instinct.

ESTROGENIC HORMONES

The word *estrogen* is used as a collective term for all substances which induce changes typical of the estrous period in the vagina, uterus, and mammary glands, and the female secondary sexual characters. The careful studies of the estrous cycle of the guinea pig, rat, and mouse, conducted between 1917 and 1922, led to the development of biologic tests for these substances and acted as a stimulus to the tremendous amount of work which has since been done on the subject.

The administration of estrogenic principles to both normal and spayed experimental animals leads primarily to a growth of the accessory genital organs. Although there are certain species differences, the main changes consist of an increase in the depth of the vaginal mucosa and its differentiation into a thick stratified squamous epithelium; the endometrium grows, presenting large numbers of mitotic figures; the uterus becomes distended by the accumulation of serous fluid; there is a pelvic hyperemia; the uterine muscle hypertrophies; the amplitude and rate of spontaneous rhythmic contractions of uterine and tubal musculature are increased; and the uterus is sensitized to the action of the posterior pituitary oxytocic hormone. In immature animals estrogen leads to the changes familiarly associated with puberty, such as establishment of the vaginal introitus, the development of the genital organs, and the manifestation of the secondary sexual characters. It is of importance, also, in the growth of the mammary glands, since it stimulates the development of the primary ducts and the epithelium covering the nipples.

In primates who menstruate, the estrogenic hormones control the development of the secondary sexual characters and the changes in the genital organs which characterize the preovulatory phase of the cycle. In both monkeys and women, they induce a growth of the endometrium, corresponding histologically with the stage of proliferation, cornification of the vaginal mucosa, hypertrophy of the uterine muscle, and development of the mammary duct system.

Several biologic tests for estrogenic hormones have been described, and they are based on the reparation of the postcastration atrophy of the accessory genital organs of small laboratory animals. By this means it has been demonstrated that estrogens are widely distributed in nature, not only in living but in inorganic matter. In mammals it is generally held that they are produced by the ovary, but there must also be an extragonadal source, possibly the adrenal gland, because they are found in the blood and urine of women after castration; and there is good reason to believe that the human placenta is concerned in their elaboration. They have been demonstrated in the liquor folliculi of normal Graafian follicles, some atretic follicles, and young corpora lutea. They are produced in very great quantities in women during gestation, and can be found readily in both maternal and fetal blood and urine, amniotic fluid and placenta. During the course of the

eggs were washed out of the Fallopian tubes immediately after ovulation, and there was no resultant interference with the succeeding menses. The demonstration of "anovulatory menstruation," in both monkeys and women, has made the dictum "Ohne Ovulation, keine Menstruation" retire to oblivion.

The role of the various hormones in the menstrual cycle is much better understood, and actual menstruation has been reproduced in spayed monkeys. It is known that the anterior hypophysis controls the function of the ovaries, the estrogens bring about the proliferative growth of the endometrium, and progesterone induces the premenstrual qualitative changes necessary for the successful implantation of a fertilized ovum. Although there is no lack of theories, mostly based on the interplay of ovarian and anterior lobe hormones, a completely satisfactory explanation for menstruation itself is still lacking. There is good reason to believe, however, that the flow is initiated, not by some positive factor acting on the uterine mucosa, but from the cessation of ovarian hormone influence. A step forward in our understanding of the mechanism actually concerned with the desquamation of the endometrium has been the study of this process in implants in the anterior chamber of monkeys' eyes and the discovery of the important part played by the fine blood vessels.

Superstitions die hard, and today many still believe that women menstruate regularly at twenty-eight-day intervals, and that estrus and menstruation are comparable phenomena. Nevertheless, ample evidence has been adduced, showing that estrus in the lower animals occurs at the time of ovulation and not at a period corresponding to that of the menses. Also, many reliable records of the length of the menstrual cycle have been published in many countries supporting the oft-quoted statement that "the only *regular* feature of menstruation is its *irregularity*."

The last two decades have seen great advances in our knowledge of the physiology of reproduction. Much remains to be done, and the work continues. It is enhanced by the development of methods of study such as biologic and chemical tests for the various sex hormones, the careful utilization of menstrual calendars, the determination of the pH of the vagina, the interpretation of vaginal smears, the histologic examination of biopsy specimens of the endometrium. These procedures are not necessarily of any value in clinical work but they are additional "tools" for investigating normal physiologic processes which must be understood before a successful approach can be made in dealing with pathologic conditions. It would not be surprising if in the next forty volumes the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY should record even much greater progress than it has in the past twenty years.

forms, the main difference between the two resting on a difference between their melting points. It also has been prepared synthetically.

A biologically inert substance, *pregnenediol*, with the molecular formula $C_{21}H_{36}O_2$, has been isolated from the urine of women in the post-ovulatory stage of the menstrual cycle and during pregnancy. It appears that this substance must be regarded as a metabolic end-product of progesterone and is excreted in the urine at a time when there is an active corpus luteum.

A more recent development of this work has been the synthetic preparation of *pregneninolone*, which is active orally, and induces physiologic effects comparable to those of progesterone.

ANDROGENIC HORMONES

A reference to the male sex hormones, the androgens, is necessary even in such a cursory review as this. These substances are sterols, closely related to the estrogens and progesterone, and they are found in the urine of women just as estrogens appear in appreciable amounts in the urine of men. The exact relationship between these various substances in normal physiologic processes still is not clear and must await further light.

The androgens have a definite masculinizing influence, acting directly on the accessory genital organs and influencing the development of the secondary sexual characters. From this viewpoint they may be regarded as the male equivalent of the estrogenic hormones.

Many substances have androgenic properties, but three are of importance because they occur naturally in the human being. Two, namely *androsterone* and *dehydroisoandrosterone*, have been obtained from urine, while *testosterone* originally was extracted from testicular tissue. The latter hormone has aroused considerable interest because of its employment with apparent success in the treatment of certain gynecologic and obstetric disorders.

THE MENSTRUAL CYCLE

The concepts of menstruation generally accepted in the early twenties were based altogether on the previous histologic studies of the German school. These had demonstrated the existence of an anatomic ovario-uterine cycle, and today they are still acceptable, although some of the original physiologic interpretations have been disproved. For instance, it was maintained that menstruation could not occur without a preceding ovulation, and that the ovum was the guiding factor determining when the menses appear.

A great impetus to the study of the menstrual cycle came with the adoption of monkeys as suitable laboratory animals. On the basis of many extensive investigations, conducted mostly in this country, it is now realized that menstruation in the *Macacus rhesus* is practically identical with this process in women. If findings in monkeys are not necessarily applicable to the human being, they at least pave the way for more discriminatory studies. The fact that the ovum exerts no control was clearly shown by a series of brilliant experiments in which

function fluctuate with alterations in the general metabolism of oxygen. I have been unable to find any critical studies of endometrial responses to thyroid therapy or any studies of ovarian levels prior to, during, and following this form of therapy. I have not observed, personally, a single instance in which intensive thyroid therapy of patients whose bleeding occurred from estrogenic endometria was followed by bleeding from progestational endometria, i.e., no proof that ovulation was induced, even in patients who presented typical signs of myxedema. Regulation of the frequency and duration of bleeding has been observed to occur independently of a qualitative change in ovarian function; this observation is compatible with a concept of a simple speeding up of metabolism. I have observed pregnancies after thyroid therapy in women, whose endometriotropic and hormonal studies indicated no ovarian failure. These occurrences have been related to the ability of thyroid substance to overcome existing gametopathic factors due to inefficient local metabolism of oxygen in the ovaries.

Chorionic Gonadotropins.—The first gonadotropins available, those prepared from pregnancy urine or placenta, despite early enthusiastic reports, have been shown incapable of inducing ovulation in ovaries not spontaneously exhibiting normal cycles. Augmentation of normal responses, as judged by the occurrence of multiple corpora lutea or by amplification of the progestational phase, may be produced by therapy with these agents. Any regulatory effects exerted upon the character of estrogenic bleeding are relatable to alterations induced in estrogenic metabolism, chiefly that of increased destruction or elimination of those substances.

Pituitary Gonadotropins.—These appear, on the basis of all animal studies, to be the logical therapeutic substances when ovarian failure results from hypopituitarism. Experience with the commercial preparations of these has been generally disappointing. All of these preparations admittedly are too low in unitage of active principles to warrant any significant therapeutic expectations. Most pharmaceutical organizations have reported little or no success in economical concentration of these extracts; other extrapituitary sources have been explored.

On several occasions I have secured definite gonadotropic responses to intensive therapy with an active pituitary powder, not available commercially, in patients with pituitary emaciation and cachexia (Simmonds' disease). These responses simulated those reported following similar therapy in the hypophysectomized female monkey; correction of genital regression, initiation of bleeding when uterine enlargement and endometrial proliferation permitted and eventually restitution of normal ovarioendometrial cycles, judged by the spontaneous occurrence of progestational bleeding.

Equine Gonadotropins.—My early experiences with gonadotropins derived from the serum of pregnant mares indicated that follicular maturation (i.e., estrogenic metabolism) was enhanced by their employment in some women with estrogenic bleeding. I failed to find any evidence that this stimulation proceeded to the point of producing ovulation. It was shown subsequently that several times the dosage required to produce follicular stimulation in the sexually mature

THE ENDOCRINE THERAPY OF FUNCTIONAL OVARIAN FAILURE

E. C. HAMBLÉN, M.D., DURHAM, N. C.

GYNCOLOGISTS relate, either by fact or by theory, many aberrations of gynecic function to ovarian failure. A great bulk of all organotherapy has been directed toward the correction of these functional disturbances of women. Enthusiastic adventures in therapy have overshadowed frequently basic failures to evaluate critically the underlying functional pathology.

The sequelae of ovarian failure vary in gravity with the time of occurrence of the failure (i.e., during adolescence, sexual maturity, and the climacteric) and with the degree of its completeness. The etiologic primacy of hypoovarian states is varied: The cause may be intrinsic to the ovaries or the ovarioendometrial system; it may be due to functional alterations in glands other than the ovaries; it may be wholly nonendocrine, as for instance, that failure precipitated by constitutional diseases, nutritional states, or local pelvic factors. Measures designed to overcome ovarian hypofunction are diverse; if these are employed rationally, they should be based upon secure diagnostic data. The ultimate choice of therapy is influenced frequently by the marital status and maternal aspirations of the patient. Except in instances of patients whose ovarian failure is due to the climacteric or to surgical or roentgenologic menopause, or under circumstances wherein the lowered fertility attendant upon the ovarian failure is not undesired by the patient, the true criterion of successful therapy is its ability to institute or restore cyclic ovarioendometrial responses compatible with the fertile state.

A critical analysis of the various therapeutic regimes yields a paucity of data regarding the *modus operandi* of individual agents and supplies little unequivocal proof that complete physiologic salvage is effected. A brief survey will be made of some of the endocrine agents commonly employed in the treatment of ovarian failure.

Thyroid Substance.—Powdered thyroid gland continues to hold a pre-eminent place in gynecic therapy. Many recent authors advise its use in the treatment of habitual abortion, endocrine sterility, and all of the various irregularities of bleeding. Most reports emphasize the high incidence of pregnancies in women with hypothyroidism or with presumed endocrine sterility following thyroid therapy, or describe the regulatory effects of this therapy upon acyclic bleeding.

In reality, thyroid substance, the earliest known active endocrine agent, has received less critical study of its gynecologic roles than any of the various gonadotropins or sex sterols isolated during the past fifteen years. Clinical and experimental data on thyro-ovarian interrelationships have suggested many conflicting theories. Perhaps, the most generally accepted one of these assumes that ovarian levels of

tational responses in patients with spontaneous ovarian failure. The use of progesterone in anovulatory failure of the ovaries does not restore normal ovarian cycles; it may complement the endocrine deficit but does not circumvent the germinal failure.

Stilbestrol.—This is a synthetic drug, not a hormone. Its estrogenic properties, its high potency when given orally, its cheapness and its established toxicity render it, in my opinion, a dangerous drug to make available for general clinical use. It has no unique role in the treatment of ovarian failure; all its desired actions may be accomplished safely through the use of naturally occurring estrogens.

Androgens.—No clear-cut role in gynecic physiology or any rational therapeutic indications in endocrinopathic gynecology have been established for these sterols. Pre-existing ovarian failure is enhanced by androgenic therapy; all of the proved pharmacologic effects of androgens are "ovarian-negating" in nature.

Cyclic Sterol Therapy.—I have established the ability of cyclic sterol therapy (estrogens followed by estrogens and progesterone or estrogens and progesterone alone) to permit effective control of estrogenic menometrorrhagia; frequently this regulation continues after cessation of therapy. Ability to control excessive bleeding in the young woman by nonsurgical means, even though this effect may be only temporary, permits important applications: (1) Cyclic bleeding may be insured while anemia and other effects of hemorrhage are repaired; (2) the remission from excessive bleeding may permit adequate therapy of hypothyroidism or the medical treatment of pelvic congestion or infection; (3) this may permit tiding a young patient over a trying period of adolescence, until nature may complete the phase of sexual maturation, i.e., initiate fertile cycles.

I have suggested that this form of therapy might yield complete therapeutic salvage despite the fact that first impressions suggest for it only a temporizing or symptomatic role. The theoretical assumptions were advanced that ovarian conditioning might be effected by means of alterations induced in the pituitary function by cyclic sterol therapy or that disturbed metabolism and utilization of sterols by the endometrium might be corrected by this type of therapy and, thereby, overcome the disturbed ovarioendometrial responses characteristic of certain types of ovarian failure. Certain observations, which I have made, suggested the likelihood that a possible endometriopathic type of ovarian failure exists: (1) Some patients excrete cyclicly moderate amounts of pregnanediol (metabolic product of progestin), and yet bleed from estrogenic endometria; (2) many patients with functional estrogenic bleeding give minimal or no progestational responses despite repeated cycles of sterol therapy; (3) patients with adolescent hypo-ovarianism who have failed to respond to equine gonadotropins may respond following intensive estrogenic therapy which has produced significant uterine hyperplasia and endometrial proliferation.

Recently my associates and I have submitted evidence that complete physiologic salvage may be effected by cyclic sterol therapy in certain patients with ovarian failure. The post-treatment endometriotropic responses of 21 of a group of 51 young patients who received a total

woman was unable to call forth any recognizable responses in the ovaries of climacteric women. I have reported that, whereas occasionally rapid and complete sexual maturation followed equine gonadotropic therapy in young women with classical hypoovarianism, the majority of these women failed to obtain any signs of ovarian stimulation. These studies, all of which formed the basis for a theory that only those ovaries, which were receptive and yet which were receiving inadequate intrinsic gonadotropic stimuli for full follicular responses (i.e., instances of ovarian failure due to hypopituitarism), were amenable to this form of therapy, were overshadowed to a great extent, by the therapeutic enthusiasm aroused by reports that normal ovarian cycles could be augmented by injections of equine gonadotropins. Two important facts were overlooked in the haste of some clinicians to adopt this new therapeutic weapon: (1) Normal ovaries do not require therapy, whereas ovaries which have failed do not necessarily preserve the receptivity of normal ovaries; (2) no proof has been submitted that even when receptivity of ovaries to equine gonadotropins exists, full physiologic responses may be induced (i.e., ovulation and proliferation of the corpus luteum), except occasionally as a part of response of certain patients with classical adolescent hypoovarianism; in other words, equine gonadotropins, even under most favorable circumstances, may not do a full job of complementing pituitary deficits.

Estrogens.—The ability of these sterols to produce sexual maturation (i.e., enlargement of breasts and genitals, and epiphyseal union) in patients with classical adolescent hypoovarianism is well known. Since no stimulation of the gonads occurs, normal physiologic ovarian cycles are not initiated and salvage of the patient for procreative functions is not effected. The fact that estrogenic therapy stops excessive or prolonged estrogenic bleeding offers a simple method for hemostasis in some instances of menometrorrhagia due to ovarian failure.

The subjective symptomatology of the climacteric is treated commonly with ovarian principles, the rationale being that of supplementing for the physiologic hypoovarianism of this physiologic epoch. The use of gonadotropins at this time is irrational, since the endocrine basis of sexual regression is the development of an intrinsic ovarian refractivity to pituitary stimuli. The desideratum of estrogenic therapy for the relief of the crises of the vegetative nervous system at this time is to mollify symptoms but not to eradicate them. Overtreatment is common at this time and results in undesired sequelae: (1) the normal processes of sexual regression may be prolonged or even halted; (2) undesired irregularities of bleeding may be produced; (3) overstimulation of climacteric endometria may favor carcinogenesis. Small amounts of estrogens by mouth often suffice to secure grateful stabilization. Only a minority of women requires any endocrine therapy. Sedatives, reassurance, and correction of environmental and social conflicts often make endocrine therapy unnecessary.

Progesterone.—Progesterone is anti-estrogenic and increases the amount and duration of estrogenic bleeding by producing further critical falls in estrogenic levels. The concomitant administration of estrogens and progesterone is necessary to secure satisfactory progres-

vaged for the reproductive function by judiciously chosen and rationally administered organotherapy.

2. Thyroid substance is most effective in patients with hypometabolism, with or without associated signs of clinical hypothyroidism. Its primary effect likely is on the germinal apparatus. Little evidence exists that marked endocrine failure of the ovaries can be overcome by thyroid substance alone.

3. The cyclic use of the ovarian sterols results in the initiation or restitution of normal ovarioendometrial responses in a certain group of patients. The ovarian failure of this group of patients has been assumed to be related to an endometriopathic factor associated with disturbances in sterol metabolism.

4. The combined and cyclic employment of equine and chorionic gonadotropins permits physiologic salvage of another group of patients, whose ovarian failure is related to hypogonadotropic activity of the pituitary.

5. Other patients, especially those whose ovarian failure is related to incomplete puerperal recovery or to the climacteric, cannot be salvaged by any of these methods of organotherapeutics.

6. At present no clear-cut diagnostic criteria have been established for selecting appropriate groups of patients for cyclic sterol or cyclic gonadotropic therapy. Ovarian responses of these patients, therefore, must be evaluated by therapeutic trials of these methods.

7. Substitutional therapy with estrogens, roentgenotherapy for excessive estrogenic bleeding or other gynecologic measures, may be more applicable to an individual patient if maternal aspirations do not render necessary an attempt to salvage the patient for reproductive functions.

REFERENCES

- (1) *Litzenberg, J. C., and Carey, J. B.*: AM. J. OBST. & GYNEC. 17: 550, 1929.
- Cooke, W. R.*: South. M. J. 24: 20, 1931. *Mussey, R. D., and Haines, S. F.*: AM. J. OBST. & GYNEC. 27: 404, 1934. *Bland, P. B., First, A., and Goldstein, L.*: J. A. M. A. 105: 1231, 1935. *Davis, C. H.*: AM. J. OBST. & GYNEC. 30: 570, 1935.
- Haines, S. F., and Mussey, R. D.*: J. A. M. A. 105: 557, 1935. *Hoffmann, J.*: Surg. Clin. North America 16: 371, 1936. *Rucker, M. P.*: Virginia M. Monthly 62: 656, 1936. *Frank, R. T.*: J. A. M. A. 109: 1861, 1937. *Litzenberg, J. C.*: Ibid. 109: 1871, 1937. *Foster, R. C., and Thorton, M. J.*: Endocrinology 24: 383, 1939.
- King, E. L., and Herring, J. S.*: J. A. M. A. 113: 1300, 1939. *White, M. M.*: Brit. M. J. 1: 62, 1939. *Allen, Edward*: West. J. Surg. 48: 1, 1940. *Novak, E.*: Ibid. 48: 6, 1940. *Thomas, E. P.*: South. M. J. 33: 744, 1940. (2) *Englebach, W.*: Endocrine Medicine, Springfield, Ill., 1932, Charles C. Thomas. *Van Horn, W. M.*: Endocrinology 17: 152, 1933. *Fluhmann, C. F.*: Am. J. Physiol. 108: 498, 1934.
- Burford, T. H., Allen, E., and Diddle, A. W.*: Endocrinology 20: 635, 1936. *Grumbrecht, P., and Loeser, A.*: Arch. f. Gynäk. 167: 199, 1938. *Schauffler, G. C.*: West. J. Surg. 46: 153, 1938. *Marine, D. A.*: Bull. N. Y. Acad. Med. 15: 790, 1939.
- Schneider, B. A.*: Quart. Rev. Biol. 14: 289, 1939. *Schneider, E.*: Med. Klin. 35: 493, 1939. (3) *Hamblen, E. C.*: West. J. Surg. 48: 300, 1940. (4) *Idem*: Endocrinology 24: 848, 1939. *Idem*: Piersol's Cyclopedia of Medicine, Philadelphia, 1939, F. A. Davis Co. 5: p. 754. (5) *Idem*: Endocrine Gynecology, Springfield, Ill., 1939, Charles C. Thomas. (6) *Hamblen, E. C.*: Endocrinology 20: 321, 1936. (7) *Watson, B. P., Smith, P. E., and Kurzrok, R.*: AM. J. OBST. & GYNEC. 36: 562, 1938. (8) *Davis, M. E., and Koff, A. K.*: Ibid. 36: 183, 1938. (9) *Hamblen, E. C.*: Endocrinology 20: 769, 1936. (10) *Hamblen, E. C., Powell, N. B., and Cuyler, W. K.*: AM. J. OBST. & GYNEC. 38: 557, 1939. (11) *Hamblen, E. C.*: Endocrinology 24: 13, 1939. (12) *Hamblen, E. C., Cuyler, W. K., Pattee, C. J., and Axelsson, G. J.*: Ibid. In press. (13) *Idem*: Ibid. In press.

of 217 cycles of sterol therapy for estrogenic bleeding, indicated that 9 of these continued to bleed cyclicly from progestational endometria (a salvage of 42.85 per cent). Two of these 21 patients subsequently became pregnant; both had remained sterile previously during their period of marriage. (None of the patients treated had clinical hypothyroidism or physical signs of any endocrinopathy.)

Cyclic Gonadotropic Therapy.—In view of the fact that complete ovarian responses were not secured in ovarian failure (except occasionally in the adolescent type) from equine gonadotropins, I devised a system of cyclic gonadotropic therapy, based on the one-two, administration of equine and chorionic gonadotropins. It was hoped that this combined therapy might complement any existing pituitary deficits. The hemorrhagenic-hemostatic responses to this therapy are not nearly as striking as those of cyclic sterol therapy. Regulation of the cycle by cyclic sterols or curettage is necessary frequently as a preliminary step to gonadotropic therapy when acyclic menorrhagia was to be treated.

The ultimate responses following completion of this therapy of a group of 10 young women who had had estrogenic bleeding can be reported at this time. Seven of these 10 patients continued to bleed rather cyclicly from progestational endometria, while another became pregnant during the first series of therapy. (This latter patient, observed for two years previously, bled habitually from estrogenic endometria and during 4 complete pretreatment cycles excreted no pregnanediol.) The physiologic salvage of this group, accordingly, was equivalent to 80 per cent. (None of the patients treated had clinical hypothyroidism or physical signs of any endocrinopathy.)

Proof that cyclic sterol therapy and cyclic gonadotropic therapy salvage different groups of patients is afforded by these observations; one of the above 10 patients, not salvaged by gonadotropic therapy, had responded previously to sterol therapy; two of the above patients, salvaged by gonadotropic therapy, had failed to respond to sterol therapy; one of the patients failed to respond to either sterol or gonadotropic therapy.

Other Therapeutic Measures.—Other measures which may correct diverse grades and types of ovarian failure include: The surgical or medical treatment of hyperthyroidism; adequate treatment of diabetes mellitus with insulin; surgical handling of virilizing tumors of the adrenal cortex or ovary; roentgenotherapy of basophilic adenoma or hyperplasia of the pituitary; the adequate treatment of any disease or nutritional error which undermines the general health; the gynecologic handling of pelvic infection, congestion, or other conditions which impair the ovarian circulation. Despite old and new reports on the subject, I cannot subscribe to the belief that ovarian failure can be corrected by roentgenotherapy of the ovaries. The end results of such therapy, I believe, are more marked grades of ovarian failure.

SUMMARY

1. A large group of women with varying grades of spontaneous ovarian failure, with the exception of those of climacteric ages, may be sal-

of each death in these three cities by committees appointed for the purpose shows, in a disquieting number of instances, that most of the catastrophes have resulted from interference with "the ample resources of nature" in the processes of pregnancy and parturition. Among such abuses are the indiscriminate resort to cesarean section and, in many cases, the unjustified employment of pelvic operative delivery. While these investigations indicate no ill results in the routine induction of labor which is being practiced by some obstetricians, usually by artificial rupture of the membranes presumably at or near full term, this procedure is sufficiently radical to warrant some comment.

CESAREAN SECTION

In 1937 and 1938, 4,298 cesarean sections were performed in Massachusetts.^{3, 4} During this time there were 128,100 births, which indicates that the doctors of this state believed it necessary once in every 29 pregnancies to perform a serious abdominal operation to complete the process of reproduction. It is extremely unlikely that the structural fabric of the women living in this commonwealth has changed much, except greatly for the better, from that of 100 years ago, when cesarean sections were performed only in the rarest instances as a last resort. Behind the appalling frequency of this operation lies the fear of the doctor, insufficiently skilled in the art of pelvic delivery and thus without the confidence that such skill affords, that in no other way when even minor complications arise can he be sure of securing living infants for his patients. If almost every cesarean section guaranteed that the baby would be born alive, such a belief might have some basis in reality, but such is not the case. Four thousand, two hundred and ninety-eight cesarean sections produced 379 dead babies; an infantile death rate of 8.8 per cent, which agrees closely with a rate of 8.5 per cent derived from a study of 3,037 cesarean sections reported by 11 American authors and collected in 1937.⁵ When cesarean section is performed for the sole purpose of obtaining a living infant, it does not compete with normal delivery and low forceps, for in 12,371 delivered thus through the pelvis in our clinic the total fetal mortality, including stillbirths and neonatal deaths, was only 3.4 per cent.

No one will quarrel with the necessity for cesarean section in cases of actual cephalopelvic disproportion. There are also occasional instances of true uterine inertia, which, resisting attempts at stimulation, make abdominal delivery much safer than violent extraction through an incompletely dilated cervix. Cesarean section is indicated in complete and partial placenta previa when the child is alive, undeformed and almost at term, but not otherwise, as a competent obstetrician may achieve delivery by Braxton Hicks' version or the use of the Voorhees' bag with equal safety to the mother. Recent opinion indicates that cesarean section in cases of complete ablatio placentae results in a much higher mortality than does the conservative method which embraces rupture of the membranes, a pack, and a tight abdominal binder. It is not

MODERN TRENDS IN THE ARTIFICIAL TERMINATION OF PREGNANCY AND LABOR

FREDERICK C. IRVING, M.D., F.A.C.S., BOSTON, MASS.

AT THE beginning of a note appended to *The London Practice of Midwifery*,¹ published in 1826, the editor of the American edition says in his introduction:

"The facts presented in the following tabular views, may be useful as having a tendency to increase the confidence of the young practitioner in the ample resources of nature, and may render him less disposed to have recourse to instruments and artificial assistance, a fault, however, not confined to the junior members of the profession."

In Table I are abstracted from this source data which represented the hazards of pregnancy and childbirth over a century ago, long before the days of antisepsis and asepsis, when doctors washed their hands after making vaginal examinations or conducting deliveries, but not before. Twenty years were to elapse before the discovery of general anesthesia; the clinical thermometer, urinalysis, the sphygmomanometer, pelvic mensuration, and prenatal care were far in the future. The second part of the same table shows the recent maternal mortality rates of three large American cities, which in two instances are the same as those from which were derived the death rates of a hundred years ago. While it is freely admitted that the vital statistics of those days may not be entirely accurate because of the difficulty which may have existed then in collecting such information, what amazes us is that modern results in obstetrics are not incomparably better. Undoubtedly certain changes in economic, social, and racial factors have played their part, but careful investigation

TABLE I

DATE		MATERNAL MORTALITY PER 1,000 BIRTHS*
1781	Westminster General Dispensary (London)	3.6
	Private Practice (Merriman's Synopsis)	5.2
1808-1815	Philadelphia, Bills of Mortality	4.5
1814-1820	New York City, Report of City Inspector	6.8
	Private practice of Dr. David R. Arnell, Goshen, N. Y.	3.3
	Average	4.7
		MATERNAL MORTALITY PER 1,000 LIVE BIRTHS
1930-1932	New York	5.8
1931-1933	Philadelphia	7.4
1933-1935	Boston	6.8
	Average	6.7

*Because of the lack of data it is impossible to determine the number of live births. From the statistical point of view such a correction would modify the figures very little.

sure against an unyielding perineum in some cases will cause intracranial damage, a fact which was recognized by Goodall⁶ in 1934. Studdiford and Salter⁷ have noted the frequency with which premature infants suffer from this cause, and their advice to deliver them by low forceps after an episiotomy is sound obstetrics. In our clinic, the policy is to deliver patients by low forceps after the scalp is showing, (1) if the fetal heart rate shows significant variations or (2) if there has been no progress for two hours. The incidence of this operation varies from 25 to 30 per cent; the fetal mortality of viable infants delivered normally is 3.7 per cent and of those delivered by low forceps 2.6 per cent.

The characteristic haste of some American *accoucheurs* to terminate labor is shown not only by their frequent resort to cesarean section but also by the readiness with which they effect operative delivery through an undilated cervix. Such an ill-advised policy can only result in laceration of the cervix with deep vault tears, prolapse of the uterus with cystocele, dissolution of the perineum, and a number of dead babies. The cautious obstetrician, if he also practices gynecology, should find little opportunity to perform plastic operations upon his own patients. Barring cephalopelvic disproportion, patience and expectancy will usually result in full dilatation of the cervix with descent of the head. Should uterine inertia set in, and there be no abnormalities of the presentation or in the adaptation of the head to the pelvis, pituitary extract given sparingly in one-minim doses will usually produce the desired effect. To those who, having had little experience with this drug, inveigh against its use, in any case even in such small amounts, with the blindness of religious zealots, we submit that we have so used it in several thousand cases not only with no bad effects upon mother or child, but, on the other hand, with uniformly good results.

THE INDUCTION OF LABOR AT TERM

The induction of labor toward the end of pregnancy, when performed for a distinct indication, is a most valuable procedure, and in pre-eclampsia it is a salutary measure for both mother and infant. Of late years, however, "delivery by appointment," usually by rupture of the membranes, for the convenience of the patient, and of the doctor, has come into vogue with certain obstetricians. Short series of cases have been reported to prove that it causes no ill effects, but no control series of cases that have not been tampered with have been published with them. In medicine, when a new policy is advocated, it is not enough to show that the results so obtained are no worse; if the innovation is an improvement the effect should be better. In 1937 Plass and Seibert⁸ reported routine rupture of the membranes in 681 cases, stating frankly that the indications were rarely medical, but that most patients were induced to shorten their ante-partum stay in the hospital. No mothers died, and there was no increase in fetal mortality or maternal morbidity. There were, however, 5 cases of prolapse of the cord,

the treatment for pre-eclampsia, eclampsia, nephritis, heart disease, tuberculosis, nor, we believe, for diabetes.

One thousand two hundred and eleven, or almost a third of these cesarean sections, were performed because of the same operation in the previous pregnancy. From 1929 to 1938 inclusive at the Boston Lying-in Hospital, 55 patients who had had previous cesarean sections were delivered 73 times subsequently through the pelvis. One patient was thus delivered 5 times, 3 thrice, and 9 twice. In no instance did the uterus rupture. One mother died of pulmonary embolism on the third post-partum day, an accident which might with equal possibility have occurred had a cesarean section been performed upon her. The maternal mortality rate, therefore, was 1.4 per cent. Four infants, or 5.5 per cent, were lost; 3 were still-born following premature separation of the placenta, and one had a spina bifida and meningocele. There were 13 deaths among the 1,211 patients, who in Massachusetts during 1937 and 1938 were subjected to repeated cesarean section, a mortality of 1.1 per cent. Although this is a low mortality rate, it is not substantially better than we obtained in our patients subsequently delivered through the pelvis. It certainly does not justify a laparotomy in every case.

ROUTINE PELVIC OPERATIVE DELIVERY

The word "prophylactic" is loosely employed in the modern American obstetric vocabulary. According to the *Encyclopaedic Dictionary* it means "defending or protecting against disease." If in the minds of some obstetricians of today the normal delivery of a baby that presents by the vertex is a disease, then "prophylactic version" and "prophylactic forceps" are good usage, but not otherwise. The policy of routine internal podalic version, which startled the obstetric world about twenty years ago, has fortunately made but little lasting impression. Thrilled by the manual dexterity of the arch apostle of this maneuver, many pilgrims returned home hoping that having but touched his mantle, they might have acquired a measure of his uncanny skill. Before long a series of lacerations in the mothers and of intracranial hemorrhages and spinal paralyses in their babies brought disillusionment. It has never been clear why anyone should wish to convert a normal vertex presentation into an abnormal pelvic one, and then to proceed with immediate extraction. Indeed, one of the notable advances has been the increased frequency with which external cephalic version has been used to correct breech presentation. Internal podalic version has a distinct place in obstetrics, but like all other obstetric operations, only on definite indications. Chief among these are prolapse of the cord after full dilatation of the cervix. At the Boston Lying-in Hospital, it was employed in only 0.5 per cent of 20,364 deliveries.

The routine use of low forceps, also, is by no means necessary. If the patient appears to be delivering her baby normally, there seems to be no valid reason to prevent her. On the other hand, prolonged pres-

CHANGES IN THE TREND OF EMBRYOLOGIC RESEARCH

GEORGE L. STREETER, M.D., BALTIMORE, MD.

IN THIS anniversary number it is perhaps not too far afield to look back at embryology as one of the basic subjects from which obstetrics and gynecology were in part derived. These lusty descendants have long since justified their own and independent spheres of usefulness, but embryology is still an underlying subject, and during the period covered by this anniversary, important advances in embryologic concepts have taken place. It is the purpose of this brief paper to outline what appears to me as an improved trend in our understanding of the mechanisms of development.

When the publication committee of this JOURNAL and its board of editors were studying embryology as medical students, great emphasis was being laid on the teachings of comparative embryology. Balfour and the Cambridge School were expounding on the elaborations of the three-germ-layer theory with great clarity. The continental investigators, taking advantage of the serial section technique, were writing extensively on the detailed structure of all manner of embryos. These studies culminated in such publications as the Hertwig *Handbook of Comparative Embryology* and the Kiebel *Normen Tafeln Series*. The burden of their writings was that there are morphologic ground plans in development and that these with various adaptations are followed in all animal forms. To them it was the pattern that was important, and this was of an ordained design. It was the concern of the investigator to discover this design, with the expectation that it would furnish the key to development. Thus the biogenic law and the three-germ-layer theory were widely accepted with the reassuring belief that nature's processes are simple when one has discovered the basic morphologic plan.

While Europe was industriously inventing doctrines and at a time when some of their embryologic tenets appeared to be permanently established, a new direction of research sprang up; and this was largely due to workers on this side of the Atlantic. The details of development were dropped and interest was concentrated on end products. The attempt was made to discover the laws of breeding and cross-breeding, and the science of animal genetics therewith came into existence. The geneticist soon settled on the chromosomes as the responsible agents for the end products and an American school, using the rapid breeding fruit-fly, the *Drosophila melanogaster*, as the test animal, accumulated a great body of observations and deductions by which the end products of development could be predicted and controlled to a remarkable extent. There was, however, no thought in this of upsetting in any way the prevalent embryologic teaching of ground plans and germ layers. These investigators were not concerned with the visible phenomena of development and were not actually handling embryonic tissues.

In the meantime interest had arisen in two other directions which did involve handling embryonic tissues. One of these is represented

which they admit is greater than the usual frequency. There is yet no evidence, when the cervix is effaced and there is some dilatation of the cervix and in the absence of cephalopelvic disproportion or of an abnormal presentation, that in the hands of a well-trained obstetrician such a procedure is often productive of harm. On the other hand, should prolapse of the cord occur, or puerperal infection set in, the attendant should be willing to accept the blame for an accident which probably would not have happened had he not interfered with a normal pregnancy.

The general practitioner, if not the obstetric specialist, may derive some comfort from the incontrovertible fact that childbirth, if left alone, is usually a normal process. In sixty years, 73,532 women have been delivered in the poorer districts of Boston by third- and fourth-year students of Harvard Medical School, with the loss of 82; a death rate of 1.1 per thousand. Up to the establishment of the Pregnancy Clinic in 1913 the rate was 1.6 per thousand; since then it has been 0.5 per thousand. During the last six years, 5,033 women have been delivered with no deaths. All abnormal cases are sent into the Hospital; no operations are performed on the District except low forceps and multiparous breech extractions. Possibly such results smack of midwifery rather than of obstetrics, but be that as it may, it is not likely that the results would have been as good if 1 in 29, or 2,604 women, had been subjected to cesarean section, if several thousands of others had been delivered by "prophylactic" version or forceps, or if the membranes had been ruptured indiscriminately simply because the patients appeared to be at term.

REFERENCES

- (1) The London Practice of Midwifery, ed. 6, Concord, New Hampshire, 1826.
(2) *Irving, F. C.*: New England J. Med. 217: 693, 1937. (3) *DeNormandie, R. L.*: Ibid. 219: 865, 1938. (4) *Idem*: Ibid. 223: 45, 1940. (5) *Irving, F. C.*: J. Connecticut State M. Soc. 1: 483, 1937. (6) *Goodall, J. R.*: Surg. Gynec. Obst. 58: 882, 1934. (7) *Studdiford, W. E., and Salter, H. P.*: AM. J. OBST. & GYNEC. 35: 215, 1938. (8) *Plass, E. D., and Seibert, C. W.*: Trans. Am. Gynec. Soc. 61: 329, 1936.

UTEROTUBAL INSUFFLATION AS A TEST FOR TUBAL PATENCY, 1920-1940

I. C. RUBIN, M.D., NEW YORK, N. Y.

UTEROTUBAL insufflation was devised in 1919 as a nonsurgical method of determining tubal patency or nonpatency in cases of sterility. It developed indirectly from previous attempts to accomplish nonoperative exploration by the injection of fluids opaque to the x-rays. Prior to 1919, collargol (Cary, Dimier, Rubin) and the halogen salts (Rubin) were used to visualize radioscopically the uterine cavity and lumen of the Fallopian tubes. These radiopaque substances had inherent disadvantages, notably chemical irritation, intratubal inspissation, and limited radiopacity in the strengths then employed.

The departure from the use of x-ray opaque substances and their substitution by oxygen was made to avoid undesirable results. Oxygen had already been introduced into the abdominal cavity by direct puncture and appeared to be well tolerated (Stein and Stewart). The insufflation of oxygen into the uterus and through the tubes was first carried out clinically in November, 1919. Certain symptoms, chiefly shoulder pains and epigastric distress which followed the insufflation, were relieved by reducing the amount of oxygen and by placing the patient in the knee-chest or Trendelenburg posture. Furthermore, from the outset some mechanical control over the pressure attending the insufflation was provided.

The indications and contraindications for the use of the new method were carefully considered. It was obvious that for clinical application every safeguard should be taken. Accordingly the volume insufflated was reduced to a necessary minimum, 50 to 150 c.c.; a siphon volumometer was added to the insufflation apparatus which already had included a manometer and a suitable uterine cannula. Vaginal and cervical hygiene, preference of the postmenstrual phase as the time of choice for performing the test, were further favorable steps.

Carbon dioxide was next substituted for oxygen, as the latter was found to cause somewhat persistent shoulder symptoms, lasting in many cases for twenty-four to forty-eight hours, unless a very minimal amount had been used (50 to 75 c.c.). CO_2 has the great advantage over O in being more soluble and more rapidly absorbed. Furthermore the use of CO_2 appeared to eliminate the possibility of embolism. Thus insufflation of an amount of CO_2 equal to that of O was found to be resorbed in a few minutes, the patient being kept in the Trendelenburg posture.

It was early recognized that a constant flow rate was useful. Accordingly, the amount of gas to be introduced was estimated by the number of seconds required to reach 100 mm. Hg (15 seconds to 100 mm. Hg). This pressure rate flow was reduced to thirty seconds to 100 mm. Hg and later on to slower rates. In the last ten years approximately, I have endeavored to use the more convenient constant flow rate of 60 c.c. per

by a group who by means of cultures in artificial media, were able to isolate individual embryonic cell masses and study their characteristics in the living state. In this way, much has been learned regarding the requirements for the survival, growth, and differentiation of embryonic tissues. The important fact was revealed that differentiation requires a sufficient mass of tissue. This signified that cells are dependent on the influence of neighboring cells and particularly on those differing from them in certain potentialities. It was also found that in tissue cultures embryonic cells possess an unexpectedly large capacity for change in form. A given tissue having the form of a delicate reticulum, such as commonly seen in embryonic connective tissue, may, with a slight variation in the conditions, take the form of a mesothelium. The student of living cells has learned to distinguish the different types by their range of transformations instead of by any permanent characteristic form. It is form-behavior rather than a fixed morphology that must be relied upon.

The other group studying embryonic tissues comprises those who, using live embryos, have removed or transplanted larger or smaller parts at various stages of development and in this way have answered questions of regeneration, the specificity of tissues and the form and orientation of individual organs and parts. This led to the discoveries of the influence of different embryonic tissues upon each other and the dominance of some over others. By appropriate stimulation, duplicate organs could be "induced." It was further found that induction of new organs did not require living inductors, but the derived chemicals were similarly effective. Also to be mentioned is the large body of observations that has been made on the hormonal factors which serve as regulators of growth and development. These appear to be in the nature of environmental influences and therefore are to be grouped with the inductor agents.

As these discoveries became available to the embryologist, he has found that a more satisfactory analysis of development can be made than the classic one of the past which was based almost entirely on an artificial morphologic ground plan. The embryo, with the opportunities now existing, can be studied as a functional organism and the activities of its constituent cells can in large part be determined. It is found that these vary with the change in complexity and with the consequent change in physiologic requirements from stage to stage. The number of layers and the form of the cavities appear to be merely incidental and what were thought to be vestiges of phylogenetic importance are now in many instances found to be temporary embryonic structures, essential to a particular period of development. The present trend in embryology is thus to regard all parts of the embryo and its auxiliary tissues as having functions to perform. The investigator endeavors to distinguish which of these functions are for the immediate maintenance of the organism and which produce actual developmental alterations. It is now realized that the embryo at all stages is a living individual, and is to be explained as a biologic problem, rather than an exercise in purely morphologic abstractions. One now begrudges the immense amount of effort that has in the past been expended on discriminating between the ectoderm, mesoderm, and entoderm cells.

phases of the menstrual ovulation cycle grouped themselves into certain patterns, while at the same time the force of the contractions could be measured in terms of mm. Hg. Experimental application of this method in the monkey in 1936, and thereafter in the rabbit, paved the way for its clinical application as a biodynamic assay of hormonal therapy. It was reserved chiefly for cases of prolonged amenorrhea and certain cases of menopause. Other substances, such as pituitrin, pitressin, pitocin, thymophysin, adrenalin, and acetylcholin, were also checked as to their pharmacodynamic action by intravenous injection in the rabbit.

In the development of the method of uterotubal insufflation during the past twenty years, a period covering the progress of this JOURNAL, many notable contributions were made by others. The limitations of space allotted to this article make it impossible to enumerate all of them.* In this brief review, however, one cannot fail to mention a few of the pioneers.

Among the first to adopt the new method were Reuben Peterson, 1921, 1922 and 1928; Dawson Furniss, 1921; John G. Clark, 1922; Robert L. Dickinson, 1922; R. S. Cron, 1922; H. Guthmann, 1922; J. J. Mundell, 1922; J. Novak, 1922; A. J. Rongy and S. S. Rosenfeld; 1922; E. Graff, 1923; S. R. Meaker, 1924. George Gray Ward established the first clinic for the specific use of tubal insufflation in sterility at the Woman's Hospital. Guthmann was the first to recognize the difference between the manifestations of pressure oscillations when the tubes were open and their absence when the tubes were closed. Henderson and Amos were the first to publish (1924) their observations on auscultatory findings during tubal insufflation, describing the tubal soufflé in patent tubes.

Many modifications of the apparatus, including a departure from the use of oxygen and carbon dioxide by substituting air, and simple devices for injecting the latter soon appeared. Some of these changes were apparently instituted to suit the needs of various conditions peculiar to different countries. Many have sought to modify the uterine cannula by additional self-retaining devices, while others assembled different types of insufflation apparatus including several for kymographic insufflation.

The French group were among the first in recent years to appreciate the value of kymographic tubal insufflation in estimating the pharmacodynamic effects of oxytocics and hormones. Bonnet introduced a quantimetric flow meter for the CO₂ and also devised a formula for calibrating the diameter of the stenosis in strictured Fallopian tubes.

Many comparisons between the value of lipiodol injection and tubal insufflation were made, while most numerous were reports on the diagnostic and therapeutic value of insufflation. A number reported upon the combination of insufflation with lipiodol injection, since Peterson and Cron employed transuterine insufflation for purposes of pneumoperitoneal diagnosis in gynecology.

*Full acknowledgment will be included in a forthcoming volume on uterotubal insufflation.

minute, which insures against undue reactions on the part of the uterine muscle and serves for comparison in the event the test is repeated for diagnostic or therapeutic purposes.

The addition of a kymograph in 1925, in which was incorporated a blow-off device for safety, enabled us to derive information that had previously escaped us. It not only provided a means of recording the graph of the insufflation (tubograph), but the pattern soon became recognizable as indicating normal physiologic function and abnormal deviations produced by underlying pathologic condition of the tubes. Thus rhythmic contractions associating normal tubal patency were differentiated from irregular, atypical contractions which characterized pathologic tubes. These atypical contractions varied both in depth of their force measured in terms of mm. Hg and in relation to their frequency and rhythmicity.

It was early observed that the pressure recorded in the case of closed tubes reached the maximum limit of 200 mm. Hg. In many instances the pressure after reaching a high level tended to drop spontaneously, which indicated a slight degree of patency. Kymographic insufflation enabled us to differentiate completely nonpatent tubes from partially patent tubes by the graphic patterns that were recorded. It moreover indicated to what extent a therapeutic mechanical effect upon the tubal obstruction was obtained and helped to distinguish uterotubal spasm from nonpatency. The kymographic insufflation apparatus has been modified since 1939 in only one respect, namely, in substituting a flow meter (Foregger type) for the siphon meter as originally employed.

The records obtained by kymographic tubal insufflation were checked at first by laparotomy observations in a series of cases and then by lipiodol injection. In practically all instances the findings were corroborated. In contrast to radiopaque substances the tubographs, properly interpreted, have the unique advantage of demonstrating in a few minutes, normal physiologic tubal function and deviations in function which are not possible by the former media.

A further step in the elucidation of the correlation between the tubograph on the one hand, tubal strictures and peritubal adhesions on the other, was to subject the dead and living organs to experimental reproduction of these conditions as far as it was possible. The dead organs were found to exert no action upon the gas which percolated through them, whereas the surviving extirpated organs demonstrated either normal rhythmic contractions under physiologic conditions and abnormal deviations under pathologic circumstances which were artificially reproduced.

It is of interest to note that rhythmic contractions are rarely observed with the naked eye during laparotomy and under anesthesia. This holds true in rabbits also, when the abdominal viscera are exposed although the intestines retain their peristaltic activity. However, when an abdominal window is sewed in, the oviducts are seen to exhibit vermicular movements.

The further development of kymographic tubal insufflation was in the field of biodynamic assay of hormones as well as oxytocic pharmacologic substances. It had been seen that the variation in tubographs at certain

in the case of nonpatent tubes; the disparity is considerable in the partially patent tube series. It is particularly in this condition where kymographic insufflation has significance.

The method of uterotubal insufflation has undergone gradual development from its incipency in 1919 to its present status as a precise and safe clinical nonsurgical test for determining tubal patency. CO₂, adopted as the gas of choice, has proved its usefulness and superiority over the years. Strict regard for clinical indications and contraindications and attention to the rules of technique are essential safeguards. The information derived from kymographic insufflation goes beyond the mere fact of tubal patency, yielding physiologic data not otherwise obtainable. It affords graphic records but, unlike hystero-graphy, no photographic films. With hysterosalpingography it shares the same limitation; namely, the necessity for correct interpretation which in the last analysis is an art acquired by ample critical experience. Without going into its comparative merits, it is fair to say that uterotubal insufflation in careful hands can be utilized without untoward immediate accidents or sequelae in all cases where it is properly indicated for diagnosis and therapy.

Bacteriologic and pathologic studies were made by some authors in connection with the general scope of uterotubal insufflation and a few articles reported the results of insufflation in the presence of adnexitis. The interstitial portion of the Fallopian tubes claimed the attention of some authors, while several studied fetal tubes and those of the newborn by insufflation. A number of reports have dealt with air embolism and a few with fatalities following insufflation. Endometrial dislocation was discussed by an occasional author and one or two dealt with insufflation during menstruation, and indications and contraindications of the method were considered.

Work upon the physiology of the Fallopian tubes during the menstruation-ovulation cycle, with and without the method of uterotubal insufflation, was reported by several authors, while a few have specifically undertaken hormonal studies in the same connection. The combination of diathermy with tubal insufflation as nonoperative restoration of tubal patency and the use of hormones for the same purpose are to be found in several publications. Study of Head zones produced by distention with CO₂ of ligated tubes and the nonsurgical reopening of ligated tubes by the same method are recent contributions. A few publications have dealt with its application in veterinary medicine.

The nomenclature of uterotubal insufflation has undergone considerable change, not only in its application in foreign lands but also in the English literature. Dawson Furniss made first reference to the Rubin test. Others have called it the Rubin method and transuterine insufflation test; while abroad many refer to it as pertubation, uterotubal persufflation, La Insuflacion tubarica, L'insufflation tubaire, Tubendurchblasung nach Rubin, and Kymographic insufflation.

The nonoperative method of determining patency of the Fallopian tubes appears to have stimulated renewed interest in the sterility problem as a whole, in the opinion of some authors, paving the way for more concentrated attention to the nonmechanical aspects.

As a result of cumulative experience with uterotubal insufflation during the past twenty years, we are now able to estimate the etiologic importance of tubal obstruction in sterility. Without going into the extensive literature on the subject, a general idea of its incidence may be obtained from an analysis of 593 replies to a questionnaire* embracing 86,113 insufflation tests performed in various parts of this country and abroad. According to these statistical data, there were complete tubal obstruction in 30.88 per cent of the cases and partial tubal obstruction in 8.85 per cent. My own series of 5,269 insufflations, the majority of which were kymographic, showed an incidence of complete tubal obstruction in 32.4 per cent and of partial tubal obstruction in 33.1 per cent.

Considering the number of authors, the variety of insufflation apparatus and individual technique, the different gases employed and the natural differences in the particular groups of patients making up the various series, it is to be expected that there will be some percentile disparity in the statistical results. Whereas, these are strikingly close

*The questionnaire was sent out in early 1939 and replies were received during 1939-1940.

fore any rational plan of maternal welfare could arise. The art and science of obstetrics has a long, a varied, and a spasmodic history. Its early course revolves around the care of the mother, and her interests were paramount and the sacrifice of the infant was often necessary. Maternal care was almost completely individual in that the midwife or doctor looked after his patient, and there was little thought of organized effort to care for the mothers of a community. Lying-in institutions were established but they were hotbeds of infection until the etiology and prevention of puerperal sepsis was determined and put into practice.

In his lectures of about 1776, Thomas Young, of Edinburgh, stated that there were two viewpoints of midwifery; one, the restricted limiting the practice to the care of the woman in labor, the other broader view encompassed the care of the woman and a knowledge of the whole field of human reproduction. He established a small hospital and made provisions for the care of women in their homes. This was in connection with the course of instruction in midwifery at the University of Edinburgh. Thomas Young was a pioneer though his name is little known. One cannot think of Edinburgh in connection with maternal welfare without calling to mind the great Simpson who did so much by establishing anesthesia and analgesia in obstetric practice. Space does not permit the mention of his numerous contributions. Antenatal care cannot be mentioned without thought of Ballantyne, also of Edinburgh, whose monumental pioneer work in this field is classic.

It is not within the scope of this article to present factual material dealing with the advancing knowledge of obstetrics. One can only hint at the devastation of human lives marked by the mute protest of the tombstones of mothers and infants of successive generations. One of the greatest killers was infection, and it took decades of accumulated experience and scientific observation on the part of men like Young, White, Gordon, Leeuwenhoeck, Holmes, Semmelweiss, Lister, and Pasteur to lay the foundations of our present knowledge of infection and its prevention.

The motives back of maternal welfare are mixed, but the objectives are clear. They may be succinctly stated as the preservation of the health and lives of mothers and babies, to minimize suffering and to maintain and improve the human race. The motives may be humanitarian or necessitarian or sentimental or materialistic. No doubt the desire for children and the falling birth rate have been potent factors among civilized races. One may view it from the standpoint of the welfare of the individual mother as the physician views his patient or one may take a broad sociologic view which embraces all mothers and all babies. What actuated Rösslein in writing the *Rosengarten* is not known, but a little rhyme in the preface of Kuhn's reproduction of the edition of 1513 is suggestive:

“For pay, I trust that I may see
That women safe and happy be,
But if such pay I am not given,
Then I must get my pay from heaven.”

THE DEVELOPMENT OF MATERNAL WELFARE ACTIVITIES

FRED L. ADAIR, M.D., CHICAGO, ILL.

THE origins of the interest in mothers and babies are locked in the unwritten records of man, and even the earliest written records only hint at the customs of early civilizations. Doubtless the instinctive behavior of males to protect their mates and of the females to save their young were manifest in primitive man. As the family and the tribe developed and as the beginnings of society were established, there were more organized efforts. There came to be patriarchal and matriarchal systems, and both male and female as well as other dieties came to be worshiped. The nomadic tribes and peoples had different mores than those who became more settled and better organized socially and economically. It followed more or less naturally that mothers and babies could and would receive more attention and consideration in the matriarchal and the communal systems. No doubt the tribes which lived in the same area for any length of time were afflicted with various types of infection. Obviously puerperal fever might have been among those disorders.

The various disorders which affected diverse members of the tribe led to various superstitions and fears and naturally the diseases which afflicted mothers were among those which eventually led to certain mores and religious rites which were designed to counteract the evil spirits which were responsible for the calamity. It is probable that in the nomadic tribes much of the care was self-care with the assistance of the husband, mothers, or some member of the family. It is unlikely that the tribal movement could be arrested by the episode of childbirth. In the communal and settled tribes those women who had experienced motherhood assumed the duty of administering care to those of their sex who were novices. Gradually this type of service fell to the lot of the older women of the tribe. This doubtless was the foundation of midwifery.

When complications arose, the assistance of the priests and the medicine man was summoned, and by means of rituals and incantations the devils were driven away and the woman survived or in case of failure she died.

The fecundity of these early peoples was high and the death rate was enormous. Living was precarious and life was cheap. The struggle for existence was difficult and sentiment played little role, the survival of the individual was apparently of little importance to anyone except himself. It is, of course, well known that weaklings at both extremes of life were frequently sacrificed, as primitive living required the self-sufficiency of the individual. We also know that abortions were frequently produced by very crude and often violent methods.

From these relatively simple tribal organizations more complex social systems arose and successive civilizations have risen and fallen leaving little trace of the development of obstetrics which was essential be-

Conference on Child Health and Protection, on various advisory committees of the Children's Bureau and those of the Maternity and Infancy Divisions of the various states. They have expended much ability and energy in making the often unpleasant but essential scientific and educational studies of maternal, fetal, and neonatal deaths. The American Committee on Maternal Welfare has replaced the Joint Committee and continues medical and nursing leadership in the field of maternal care by such activities as the publication of small obstetric manuals, pamphlets, and a quarterly bulletin. It has also created and sponsored the educational feature movie, "The Birth of a Baby," and the First American Congress of Obstetrics and Gynecology.

Various local organizations such as the Lobenstine Clinic, the Maternity Centers of New York and of Chicago, the Frontier Nursing Service, and many others have assumed national significance. The most comprehensive national program had its beginnings in the Sheppard-Towner Law which was attacked and finally failed to receive federal appropriations. Similar and even more far-reaching legislation has been incorporated in Section V of the Social Security Act which has stimulated and put into effect educational, service, and research activities in the fields of maternal and infant health in various states and territories. All of these factors and many others have been responsible for the gratifying reduction in maternal mortality rates. There is more to be accomplished and morbidity as well as mortality must be considered. The stillbirth and neonatal death rates must be reduced and morbidity must be prevented.

Medical and nursing service, education, and investigation are vital, and programs must be developed locally to meet community needs. The basic principles are general, but their application must be developed and made by methods which are best adapted to the various localities.

The mania for war should not lead us to a neglect of the vital defenses of the mothers, the home, and the motherland.

There is, so far as my knowledge of the literature reveals, no complete exposition of the fundamental principles of maternal welfare until the little known but comprehensively and beautifully written book of William Buchan was published in 1803. His work was designated for the intelligent lay reader and was entitled *Advice to Mothers*. He presents in a lucid style most of the basic ideas which are accepted today as the essentials of maternal welfare. Naturally one would not accept the methods and technique of his day as advisable today. A couple of quotations from his introduction are pertinent to this discussion. Speaking of mothers he writes, "The want of proper instruction at an early period of life betrays them into a variety of fatal mistakes respecting their own health as well as that of their children." With reference to a general plan to reach all mothers, especially those living in poverty, he states, "I do not know any manner in which humanity, charity, and patriotism can be more laudably exerted, or even a part of the public revenue more usefully employed than in enabling mothers to bring up a healthy and hardy race of men, fit to earn their livelihood by useful employments and to defend their country in the hour of danger."

Pinard stressed the importance of the obstetric examination of pregnant women, and certain institutions were established in France for their care. This was about the beginning of the present century. At this period Ballantyne was establishing prematernity wards for the antepartum care of women with complications, and he prophesied in an imaginary conversation that by 1940 the obstetricians would wonder why those of a generation before had spent so much time and thought about the few hours of labor and so little concerning the nine months of pregnancy. This has been realized in our country and even further advances have been made, as complete maternal care is now recognized not only as desirable but as essential for the future welfare of our nation. Present events intensify this feeling as the future of our civilization depends upon us, while forces beyond our control are wrecking the civilizations of Europe. We have extended our ideas of maternal welfare to include preconceptional care as shown by legal requirements for premarital examinations and for the inclusion of the father in the educational and welfare program. The family is the social unit, and the mother is becoming to be recognized as the keystone in the arch of family welfare.

One can briefly mention some of the important events in the development of maternal care from the early beginnings of prenatal work in Boston under the leadership of Mrs. Putnam, the establishment of the Society for the Study and Prevention of Infant Mortality out of which the Joint Committee on Maternal Welfare originated. From this committee, formed twenty years ago, has come national, state, and local leadership in developing programs to conserve health and lives of the mother, the fetus, and the newborn. Its members have done noteworthy work in supplying medical leadership all over the United States, have worked hard, cheerfully, and voluntarily on Hoover's White House

the support of an infant unless they have families which are financially able and willing to take the child into their family? This is often not the case.

There seems to have been a definite trend toward a gentler and more merciful attitude on the part of the law toward both the unfortunate unmarried mother and her child. In a decision rendered in one of the courts of the State of Illinois, the following expression seems significant: "The harsh doctrines of the common law which gave an unmarried mother and her illegitimate child little standing or protection, have been modified by the legislature and court decisions of this state."

The very sane conclusion of the excellent study from which I have quoted is that "the child born out of wedlock should be considered first as a child, and accorded at least an approximation of the rights accorded other children." During a service of two years on a committee of the Chicago Council of Social Agencies, which tried to draw up an improved adoption law for the State of Illinois, I was struck with the fact that the infant is not yet adequately protected. As most adoptions are of illegitimately born children, this primarily concerns this group of children. In adoptions, the interests of the child demand that a home be found which is suitable for the child rather than to find babies for homes which are childless. In some cases the latter motive seems to be the ruling one. Adequate protection of the child to be adopted should be provided in all states.

The question which particularly interests physicians is the medical care which this group should receive. Hans Zinsser of Harvard, in his recent book, speaks of the doctor as being so conditioned, by his training, that he is indifferent to social status, morality, or even criminality in those who come under his hand as patients. The unwed expectant mother, to him, is a pregnant woman who presents exactly the same obstetric problem which her more fortunate married sister does. The care of both the mother and the infant afterward may be, and in many cases is, a social problem, to be dealt with by those who are competent in the field of social service. There is a clear-cut need for both efficient medical care and competent help in making such social adjustments as may be needed.

Many illegitimate births have been cared for in "maternity homes," the efficiency of which varies greatly. Some of these are, or have been, poorly run, providing medical care of a mediocre sort. From the point of view of the physician, nothing seems adequate, or just, but proper obstetric care of the sort which may be had in a well-staffed hospital. It should be said that most hospitals have been willing to undertake their fair share of this task. Some facts are quoted in the University of Chicago Report to which I have already referred. The great majority of the hospitals which answered a questionnaire as to their attitude toward the unmarried mother responded that they cared for them. During the year 1928, 877 illegitimate babies, out of 1,346 labors, were born in hospitals in Chicago, while, in the rest of the state, only 283 labors out of 1,035 were cared for in hospitals. In the city of Chicago a few institutions did the bulk of the work, seven hospitals having cared for 655 cases.

THE UNMARRIED MOTHER AS A MEDICAL AND SOCIAL PROBLEM

W. C. DANFORTH, M.D., F.A.C.S., EVANSTON, ILL.

THE mode of dealing with the unmarried mother and her child has come down from The English Poor Law and the English Property Law. In earlier days the bearing of an infant outside of wedlock was not considered an offense against the criminal laws, but the bringing into the world of a child who might become a burden upon the parish in which it was born was an offense. In other words, having a child without being married was not legally wrong but the producing of a child who might add to the sum of public expense was against the law. This attitude, not greatly modified by the passage of time, continued until the beginning of the twentieth century. The changes, legal and otherwise, which have come about, have been largely motivated by organizations of women, who have recognized that the older view of this problem was too severe and that it did not serve the best interests of society.

The first move in our own country toward a change in attitude seems to have been the publication in 1920, by the Federal Children's Bureau, of the first of a number of studies on "Illegitimacy as a Child Welfare Problem." These have done a great deal of good in emphasizing the fact that, in cases of illegitimacy, there is always an infant, which is wholly innocent and has rights, legal and moral, to consideration. I would quote in this connection from a publication of The School of Social Service Administration of the University of Chicago, which deals comprehensively with the question of illegitimate births in the State of Illinois during the year 1928. We find in that year, in a state with more than seven million people, there were 129,668 births. Of these, 2,381 were illegitimate, or 18.36 per thousand. This study indicates clearly that the problem of the unmarried mother and her infant is one of youth, 84 per cent of the mothers being under twenty-five years of age. Forty per cent were under eighteen years, and 11.06 per cent were fifteen years of age or less. Only 7.05 per cent were over thirty years of age. From the standpoint of the most rudimentary humanity, it seems obvious that, if, in one state in one year, there are 2,381 births out of wedlock, and if 146 of these mothers are girls of fifteen years or less, and 787 more of them are from sixteen to eighteen years of age, we have before us a situation which merits the most careful consideration, not only of social workers and physicians, but of every intelligent and socially minded citizen.

The mother and the baby must both be cared for. The insistence which has been made by certain social workers that in all cases the mother be made to keep her child, seems in the face of figures such as those just given, to be ridiculous. What can a child under fifteen, or even the large group of mothers between sixteen and eighteen, do for

obstetric care, and an efficient attempt to restore the child to psychic normality, than these young girls who have been so unfortunate as to find themselves among the unwed expectant mothers.

The leaders in obstetrics in this country believe that the expectant mother and her infant should have the care which is due them. They do not condone immorality, and they regret that any woman, and particularly a young girl, should be in such a predicament. The broadening of human knowledge has brought with it great changes in the manner of dealing with the problems of society. The inadequate and sometimes brutal treatment accorded to the insane in previous centuries has given way, with the development of the science of psychiatry, to a finer, more humane and much more efficient mode of treating those afflicted with diseases of the mind. The increase in the understanding of criminology has changed very greatly the mode of dealing with those who have fallen afoul of the law. The older, more severe, and often ineffective punishments have given way to a more constructive policy in which the desire for rehabilitation finds expression. Those who have fallen victims to alcohol and drugs are helped to regain control of themselves. The effort is sometimes successful and sometimes not, but the desire to help these unfortunates back to normal life is better than a universal condemnation. And success has sometimes paid excellent dividends. The change in the attitude toward the unwed mother and her child, and the presence of the latter must never be forgotten, is another evidence of the wiser, more tolerant, and more constructive attitude of mind which has come with the passing years. The doctor with entire sympathy looks upon the unmarried mother and her child as a problem, both medical and social. Social adjustments can best be made if the mother and her child are in good physical condition. This is most likely to be if obstetric care has been adequate. All of these women cannot be made into valuable members of society. All of the members of the other groups mentioned earlier in this paper may not be fully restored to usefulness. But many can and any physician who has had large experience knows that, in spite of prejudiced statements to the contrary, some may be made into useful women. The fact that so many of them are very young makes it even more important that they should be given a fair chance. May we hope that increasing improvement in social and economic conditions may cause the number to be less in the future.

While insisting that the obstetric care extended to the unmarried mother and her infant be adequate in quality, neither physicians, who have had experience with these cases, nor social workers, are disposed to insist that all unmarried mothers are wholly worthy women. There are among them some who are irresponsible, lacking in morals and often in intelligence. It is often difficult to make anything more of them than they appear to be at first. Obstetric care and subsequent social help must, however, be given. The social worker, in such cases, has the more difficult task.

Our present economic situation probably is responsible for at least some of the illegitimate pregnancies which occur among girls of a much higher social group. The impossibility of supporting a wife and family upon the income of many young men interferes with marriage and the establishment of a home at an age at which it is physiologically desirable. This, unless young people are entirely separated, and hormonal stimuli being what they are, inevitably leads to an occasional pregnancy. These young mothers may be girls of education, breeding, refinement, in every way capable of fulfilling the responsibilities of wife and mother. Indeed, their potential worth to society may be greater than that of some of those who condemn them most severely. I, and no doubt many of the readers of this JOURNAL, have seen young women pass through an experience of this sort and later occupy useful and respected positions in their respective communities as wives and mothers. The girl should be persuaded not to have an abortion done. It is dangerous and it evades the situation too easily. The man may be more than willing to adopt a course which will immediately free him from embarrassment and all of the danger of which is borne by the girl. She is partly responsible for the existence of the unborn human being, and she should give it a fair deal and not take its life. Abortion is merely adding to the wrong already committed another of greater degree. The difficulty may be solved sometimes by sending the expectant mother to some other place, where the infant may be born, and, if necessary, adopted. The mother may then return without harm to her reputation. This device is somewhat more likely to be useful in the case of the unemployed girl whose parents have some means and who may make it possible for her to live away from home for the necessary time.

The two things which must be accomplished in any illegitimate pregnancy are the safeguarding of the health of the young woman and the preservation of her self-respect. She should be brought back to normal life in good physical condition and with her morale intact if possible. And she should not return, particularly if she is to work, until her strength is entirely restored.

In the case of the very young child, it is difficult to condemn her severely. The blame rather rests upon faulty care and supervision for which the parents are to blame. To assume that she is irreclaimable is an evidence of prejudice rather than justice, especially as young male offenders are labored with in the hope of making useful citizens of them. From the viewpoint of the obstetrician, it is difficult to imagine a group of patients who are more completely in need of proper

flow and cervical mucous contaminations excepted). Thus, a depletion of glycogen in the vaginal epithelium favors a higher pH and a more suitable nidus for the infection.

The laborious and meticulous methods used by Hesseltine⁶ to obtain pure cultures were fruitless. Yet, within the past year Plass and Trussell⁷ succeeded in obtaining a bacteria-free trichomonad culture which has been carried through numerous transplants. Plass and Trussell,⁷ by inoculating human vaginas with these subcultures, produced symptoms similar to and findings comparable to the clinical entity of vaginal trichomoniasis. Hesseltine has examined the Plass-Trussell Cultures 2 and 29 and concurs in the bacterial purity. Fragmentary evidence points to absence of viruses. Using these bacteria-free cultures, Wolters and I⁸ produced vaginitis as described by Plass and Trussell but not in as great a frequency. This outstanding feat of obtaining a bacteria-free, readily growing culture may break the "log jam" of controversy and open avenues for improvement in therapy. Even so some points are unanswered, namely: (1) under what conditions will vaginitis occur? and (2) why is there an altered bacterial flora when the condition of vaginal trichomoniasis develops?

DeLee⁹ published the first report in the American literature in 1920 on vaginal trichomoniasis in which he cautioned against confusion with gonococcal infection, described the macroscopic appearance, emphasized the need of moist slide examinations for diagnostic confirmation, but he was misled in the ease with which the condition could be cured. He relied upon a single or occasionally two or three vigorous scrubblings of the vaginal walls, followed by packing with glycerin and soda. In due time, Mathieu¹⁰ confirmed Greenhill's¹¹ procedure which deviated only slightly from the one DeLee used. Ultimately this painful and traumatic therapy became less popular and has been practically discarded.

Davis and Colwell,¹³ and Davis¹⁴ presented a scientific and noteworthy *in vitro* study of many agents for trichomonadicidal action and then made clinical applications. Their less irritating and less painful cleansing of the vagina with liniment of soft soap and antiseptic powder, creosol douche, and ichthyol glycerin tampons loomed promising. Yet Davis warned that persistent treatment for months may be necessary to effect a cure.

Many methods came before the profession with assuring promises too often based on insufficient numbers and inadequately controlled cases; but as requirements for longer periods became obvious, milder and saner practices arose. Kleegman¹⁵ introduced Lassar's paste. Furniss¹⁶ proposed diluted mercuric chloride douches. Gustafson¹⁷ urged sodium bicarbonate douche and glycerin-soda tamponade. The employment of a dry preparation (kaolin, sodium bicarbonate and stovarsol) appealed to Gellhorn.¹⁸ Perhaps to him should go the credit for fostering the dry principle advocated generally today. Still more materials and vehicles had to pass the test, such as hypertonic saline douche by Rosenthal, Schwartz and Kaldor;¹⁹ silver picrate by Winther;²⁰ quinine by Pattyson;²¹ magnesium and copper sulfate by Ruble;²² halogenated quinolines by Huffman.²³ Zener,²⁴ Janeway,²⁵ and Karnaky;²⁶ various arsenical preparations and finally common sugars

VULVAL AND VAGINAL MYCOSIS AND TRICHOMONIASIS

H. CLOSE HESSELTINE, M.D., CHICAGO, ILL.

WHEN the first issue of the *American Journal of Obstetrics and Gynecology* appeared in October, 1920, the clinical entities of vulval and vaginal mycosis and trichomoniasis were unrecognized except by a very few. Within two decades nearly every member of the medical profession of the United States has learned more about these conditions than was known by the earlier best informed specialist. Formerly the belief was current among women that vaginal discharge was associated with marriage and childbearing. Relief, but usually not cures, came from self-prescribed daily douches. This no longer holds largely as the result of scientific study. The major contributions have been made by researchers in the United States. The limited space afforded here necessitates the selection of representative works.

TRICHOMONIASIS

Vaginal trichomoniasis is an infection (until recently called infestation) caused by protozoa, or bacteria in association with the flagellate. Because Donn  identified the vaginal tetratrichomonad in 1837, his name is often associated with it. Controversies over the exact etiologic agent have waxed and waned. Musgrave¹ in 1922 commented that "the part played by the flagella in its (cystitis) production has not been sufficiently studied."

Stein and Cope^{2, 3} presented evidence supporting the contention that the trichomonads were pathogenic and recorded that no specific or other bacteria were found. Present-day views agree to the extent that the bacterial flora is not normal; that it is Type 2 or 3. Hibbert⁴ transferred vaginal discharge containing trichomonads to normal vaginas, and subsequently introduced a streptococcus with a resultant vaginitis. He assumed the streptococci were pathogenic but did not account for the inability of the bacteria with the trichomonas discharge to produce a reaction. Later Hibbert and Falls⁴ obtained favorable therapeutic results with bacterial filtrate.

With a culture of trichomonads free from bacteria and viruses, one could make experimental studies which might answer the question of pathogenicity. Generally, protozoologists have inclined to the view that bacteria may be responsible while most clinicians took the opposite stand. It is possible that it is a combination of both protozoa and bacteria (symbiotic relation) or either.

Bland, Goldstein, Wenrich, and Weiner⁵ found a variable behavior of different trichomonad strains. Their cultures grew better above pH of six and well on the alkaline side. It is established that the normal vaginal pH ranges from 4.0 to 5.5 and that the acidity is related to the carbohydrate content of the vaginal epithelium (menstrual and lochial

Most of the commonly accepted and employed preparations contain some carbohydrate or glycerin and gelatin for the vehicle or carrying agent and vaginal bacilli thrive in the presence of these, bringing about an increased acidity which is associated with an unfavorable environment for the protozoa and the abnormal bacterial flora. Hence, a direct relationship exists with the vaginal bacilli, glycogen-like content of the vaginal epithelium, increased vaginal acidity and health of the vagina. Moreover, vaginal trichomoniasis is not encountered in vaginas with a rich glycogen-like store and a thick epithelium. Since there is no evidence at hand which suggests that a pathologic hyperacidity ever exists in the vagina, alkalies should be persistently and insistently avoided.

Vaginal trichomoniasis therapy thus falls into two categories, active and supplementary. Active is that which is directed at eradication of the vaginal condition, and supplementary that which serves to prevent reinfection.

VULVAR AND VAGINAL MYCOSES

Yeastlike fungi are the only common fungi producing vulvar and vaginal mycoses. Clinicians by common usage call them monilia and cryptococcus, although the term monilia is botanically incorrect. Practically all the other fungi (leptothrix, streptothrix, actinomyces, blastomyces, etc.), irrespective of the higher, lower, or intermediate forms, produce rarely obstetric or gynecologic disease.

Within less than a score of years, the profession has become cognizant of the common vaginal mycoses of pregnancy and the mycotic vulvitis associated with diabetes mellitus. Formerly these were considered rare and of questionable import. Moench,³⁵ C. H. Davis,³⁶ Popoff, Ford and Cadman,³⁷ and Heard³⁸ contributed to the rediscovery of this entity. Plass and co-workers³⁹ characterized the clinical entity by an invariably and constantly present symptom, pruritus, and the common finding of caseous-like material or thrushlike spots in the vagina. Even though the vulva may show considerable reaction, the vagina is the focal site and usually more definitely involved. Other symptoms and findings varied considerably. The pruritus varied from a mild to a most demanding and unrelenting itch, even to the extent of severe sleep disturbances. The acme of the itch coincided with the retiring period and early hours of sleep. It was felt⁴⁰ that the pruritus resulted from some by-product of metabolism, such as acetaldehyde or pyruvic acid. Histopathologic³¹ study revealed only a superficial involvement of the vaginal epithelium.

Because many women may harbor these fungi without symptoms or clinical evidence of infection, evidence is at hand for the recognition of carriers. To advance proof of pathogenicity Plass and co-workers inoculated pure cultures of this fungi into (1) normal fungus-free vaginas with a resultant mycosis and (2) normal oral cavities of newborn infants with subsequent typical thrush states and fulfilled Kiech's postulates throughout. Later Bland, Rakoff and Pineus⁴¹ amply confirmed these responses to inoculation.

and especially lactose. The postmenopausal case will respond especially well to estrogenic hormone, so said Davis.²⁷

Like his many contemporaries, Karnaky²⁶ has changed from one to another preparation. In controlled series evaluating lactose (alpha or common), it was found²⁸ that it gave just as favorable responses as the proprietary products. The addition of citric acid was without value and hence is no longer advised. Roblee²⁹ found beta lactose equally as good. Glassman³⁰ stated that "the multiplicity of treatment indicates that a satisfactory method is not available." Surely he meant that a simple, rapid, and invariably dependable method was not at hand, for by thorough and complete treatment with one of many preparations most patients are benefited ultimately.

Cures appear to result:

1. From desiccation of vaginal mucosa with powders or tablets.
2. By protection of the deeper or basal epithelium by escharotic action of the surface epithelium.
3. From stimulating the epithelium after the menopause with estrogenic agents to build up into a healthy state.
4. By enhancing a normal epithelium and bacterial flora and replacement of a carbohydrate.
5. By a combination of actions.

All useful therapies by one or another means favor the restoration of a normal vagina, histologically, chemically, and bacteriologically.

Active therapy consists of office and home procedures. The details of the various routines are available in the current literature. Supplementary therapy is the eradication of extrinsic and intrinsic focal sites such as vaginal submucosal lesions, cervicitis, urethritis, cystitis, gastrointestinal or buccal infections, and infections in the sexual partners.

Histologic observations by Adair and myself³¹ revealed inflammatory sites and suppuration areas under the vaginal mucosa. Only bacteria were observed, but these multiple lesions might prevent physiologic recovery if therapy was prematurely withdrawn. The ordinary cervical erosions and chronic nonspecific cervicitis respond to desiccation and cauterization by chemical and electrical means, provided it is done under proper indications and with sufficient caution and judgment. Even though several workers believe that the vaginal trichomonads are not found in the rectum, anal hygiene should be prescribed as a precaution. More convincing evidence is needed to establish this point. Sexual abstinence is urgent, because in infrequent instances patients may be reinfected by their partner, according to Cornell and Riba,³² Drummond,³³ Karnaky,²⁶ and Adair and myself.³¹ If reinfection follows coitus, the male should be studied.

Because many patients with early and mild vaginal trichomoniasis are cured rather readily, extensive studies for focal sites are ordinarily unnecessary, but in instances of persistent or recurring infections, one should make a thorough search. Acidification of the urine and forced fluids may correct a lower urinary tract infection, thus excluding the need for cystoscopy. Allen and colleagues³⁴ and others called attention to this nidus.

found that single prophylactic applications immediately after birth of 1 per cent aqueous gentian violet to the oral cavity of the newborn whose mothers have vaginal mycoses will reduce remarkably the sporadic cases of oral thrush.

SUMMARY

Twenty years ago gross ignorance prevailed on vaginal trichomoniasis and vulvar and vaginal mycoses. Today these conditions are usually recognized and adequately treated although improvement in therapy should and will likely take place. To the physicians of the United States goes priority for most of the important contributions in the understanding of these entities and credit for resourcefulness in the development and improvement of therapies.

REFERENCES

- (1) *Musgrave, Wm. E.*: J. A. M. A. 79: 2219, 1922. (2) *Stein, F.*: AM. J. OBST. & GYNEC. 24: 348, 1932. (3) *Stein, F., and Cope, E. J.*: Ibid. 22: 368, 1931. (4) *Hibbert, G. F., and Falls, F. H.*: Ibid. 36: 219, 1938. (5) *Bland, P. B., Goldstein, L., Wenrich, D. H., and Weiner, E.*: Am. J. Hyg. 16: 492, 1932. (6) *Hesseltine, H. Close*: AM. J. OBST. & GYNEC. 26: 46, 1933. (7) *Plass, E. D., and Trussell, R. E.*: In press. (8) *Wolters, S., and Hesseltine, H. Close*: Unpublished. (9) *DeLee, J. B.*: Illinois M. J. 37: 186, 1920. (10) *Mathieu, A.*: Northwest Med. 29: 15, 1930. (11) *Greenhill, J. P.*: J. A. M. A. 96: 1862, 1931. (12) *Davis, C. H., and Colwell, C.*: J. A. M. A. 92: 306, 1929. (13) *Davis, C. H.*: AM. J. OBST. & GYNEC. 18: 575, 1929. (14) *Kleegman, Sophia*: Surg. Gynec. Obst. 51: 552, 1930. (15) *Furniss, H. D.*: AM. J. OBST. & GYNEC. 20: 93, 1930. (16) *Gustafson, G. W.*: J. Indiana M. A. 23: 81, 1930. (17) *Gellhorn, J. A.*: M. A. 100: 1765, 1933. (18) *Rosenthal, L., Schwartz, L. S., and Kaldor, J.*: J. A. M. A. 105: 105, 1935. (19) *Winther, N.*: Minnesota Med. 19: 731, 1936. (20) *Pattyson, R. A.*: New York State J. Med. 37: 41, 1937. (21) *Ruble, W. K.*: Northwest Med. 33: 14, 1934. (22) *Huffman, J. W.*: Am. J. Surg. 30: 312, 1935. (23) *Zener, F. B.*: Northwest Med. 36: 7, 1937. (24) *Janeway, M. M.*: New York State J. Med. 35: 528, 1935. (25) *Karnaky, K. J.*: Med. Rec. & Ann. May, 1926. (26) *Davis, M. Edward*: Surg. Gynec. Obst. 61: 680, 1935. (27) *Hesseltine, H. Close*: J. A. M. A. 109: 768, 1937. (28) *Roblee, M. A.*: J. Missouri M. A. 34: 285, 1937. (29) *Glassman, O.*: J. A. M. A. 102: 1748, 1934. (30) *Adair, F. L., and Hesseltine, H. Close*: AM. J. OBST. & GYNEC. 32: 1, 1936. (31) *Cornell, E. L., and Riba, L. W.*: Surg. Gynec. Obst. 63: 511, 1936. (32) *Drummond, A. C.*: Am. J. Surg. 31: 98, 1936. (33) *Allen, E., Jensen, L. B., and Wood, I. H.*: AM. J. OBST. & GYNEC. 30: 565, 1935. (34) *Moench, L. M.*: Med. Clin. North America, May, 1929, Philadelphia, W. B. Saunders Co., p. 1581. (35) *Davis, C. H.*: AM. J. OBST. & GYNEC. 18: 716, 1929. (36) *Popoff, N. W., Ford, F., and Cadman, W. H.*: Ibid. 18: 315, 1929. (37) *Heard, E. L.*: Texas State J. Med. 24: 357, 1928-1929. (38) *Plass, E. D., Borts, I. H., and Hesseltine, H. C.*: AM. J. OBST. & GYNEC. 31: 320, 1931. (39) *Hesseltine, H. Close*: Ibid. 34: 855, 1937. (40) *Bland, P. B., Rakoff, A. E., and Pincus, I. J.*: Arch. Dermat. & Syph. 36: 760, 1937. (41) *Hesseltine, H. Close, and Campbell, L. K.*: AM. J. OBST. & GYNEC. 35: 272, 1938. (42) *Woodruff, P. W., and Hesseltine, H. Close*: Ibid. 36: 467, 1938. (43) *Benham, R. W., and Hopkins, A. McH.*: Arch. Dermat. & Syph. 28: 532, 1933. (44) *Hopkins, E. W., and Hesseltine, H. Close*: J. Lab. & Clin. Med. 21: 1105, 1936. (45) *Stovall, W. D., and Bubolz, A. A.*: J. Infect. Dis. 50: 73, 1932. (46) *Shaw, F. W.*: J. Lab. & Clin. Med. 20: 113, 1934. (47) *Jones, C. P., and Martin, D. S.*: AM. J. OBST. & GYNEC. 35: 98, 1938. (48) *Weidman, F. D.*: Arch. Dermat. & Syph. 19: 867, 1929. (49) *Davis, M. Edward, and Pearl, S.*: AM. J. OBST. & GYNEC. 35: 77, 1938. (50) *Noonan, W. J., and Hesseltine, H. C.*: J. Lab. & Clin. Med. 21: 281, 1935. (51) *Hesseltine, H. C., and Hopkins, E. W.*: Ibid. 21: 288, 1935. (52) *Hesseltine, H. C.*: AM. J. OBST. & GYNEC. 34: 439, 1937. (53) *Burns, G., and Hesseltine, H. Close*: Unpublished.

Plass and co-workers³⁹ pointed out, also, the fallacy of the term, diabetic vulvitis, and offered convincing proof that it is actually a mycosis. Studies later by Hesselstine and Campbell⁴² terminated in emphatic confirmation of this stand. The severity of the vulval mycoses in diabetes is related usually to the degree of glycosuria. Furthermore, the vulva has a hyperemic and "scalded" appearance and lacks the caseous material or thrush patches characteristic of vaginal mycosis. The vaginal mycosis of pregnancy and vulval mycosis in diabetes thrives, presumably due to the increase carbohydrate availability of the vaginal mucosa and the glucose in the urine adhering to the external genitals.

Woodruff and I⁴³ found that the incidence of vaginal fungi (both pathogenic and carrier states) in unselected pregnant patients varied from 14 per cent in better class white to 33 per cent poor class white and to 41 per cent colored groups.

Benham and Hopkins⁴⁴ made the surprising discovery that 18 per cent of healthy women harbored these monilia in the gastrointestinal or genital tract. The incidence is lower in men. Dissemination by coitus is unlikely but occurs occasionally.

Fermentation and morphologic studies are a reliable means of identification in most instances if the detailed plan of Hopkins and myself⁴⁵ is carried out. Stovall and colleagues,⁴⁶ Shaw,⁴⁷ Jones and Martin,⁴⁸ Weidman⁴⁹ and many others have offered their views in this controversial field of identification and are recognized authorities.

Untreated vaginal mycosis of pregnancy practically always runs a self-limited course, terminating at or after delivery, presumably due to an insufficient carbohydrate content after parturition, a behavior noted by Davis and Pearl.⁵⁰

Because mycotic vulvitis occurs so commonly in diabetics, diabetes must be suspected until completely excluded by adequate tests, whenever vulvar mycosis is encountered.

Treatment of mycotic vulvitis consists of diabetic management and local fungicidal therapy. Topical application of 1 per cent aqueous gentian-violet solution daily will usually give complete relief. Applications of diluted Lugol's solution every day or so in increasing strength will likewise cure.

Vaginal mycoses respond to daily applications of 1 per cent aqueous gentian-violet solution if precautions are employed to prevent reinfection, especially from the bowel. The work of Noonan and Hesselstine⁵¹ and Hopkins and Hesselstine⁵² pointed out that acids and alkalis are therapeutically not feasible and that element iodine possessed the greatest potency in the presence of serum and cellular elements.

With this information a study was begun⁵³ and is still in progress in which potassium iodide (0.213 Gm.) and potassium iodate (0.035 Gm.) each are dispensed now in separate (0.5 to 1.0 Gm.) tablets (vehicle of neutralized Kaolin) for vaginal insertion. Vaginal acids react with these two materials to liberate element iodine thus reducing the number of office visits. Gelatin capsules provide a substitute for tablet forms, but sugar and starch vehicles must be avoided. An occasional patient complains of irritation and an infrequent one will have slight vaginal burns from the iodine. Burns and I⁵⁴ have

the acute anoxic episode at birth, it tends to circumscribe unduly the scope of the problem; in this connection it should be remembered that careful prenatal care and judicious conduct of labor will do more to save babies from apnea at birth than all the resuscitating measures in the world.

In view of these facts, the simple term *apnea neonatorum*, which is merely descriptive and carries no implication in regard to etiology, seems preferable to the older designation. The use of the word *asphyxia* could then be restricted to those cases in which apnea was actually due to lack of oxygen as in, for instance, prolapse of the umbilical cord and premature separation of the placenta.

ETIOLOGY AND PREVENTION

Cerebral Hemorrhage.—There is general agreement that the most common cause of fatal apnea at birth is cerebral hemorrhage. Statistics also concur in showing that such hemorrhage is most often consequent upon traumatic operative delivery. The procedures which are most likely to produce it are, in order, version and extraction, midforceps delivery and breech extraction (it being assumed that high forceps, which would otherwise head the list, is an abandoned operation). The prevention of grave apnea neonatorum, accordingly, consists very largely in the avoidance, when possible, of these operations.

Although clinical and necropsy evidence shows that trauma is the deciding factor in most of these hemorrhages, it is well known that all newborn infants show an especial tendency to bleed and it seems probable that this diathesis plays an auxiliary role, at least, in some of these cases. A rational explanation for this hemorrhagic tendency was advanced in 1917 by Brinkhous, Smith and Warner who showed that the plasma prothrombin level of babies at birth is exceedingly low, ranging from 14 to 39 per cent of the usual adult value. During the past two years Hellman and Shettles, of the Johns Hopkins Hospital, have been exploring the possibility of raising the low plasma prothrombin of the newborn infant by administering vitamin K antenatally to the mothers. They have shown, beyond peradventure, that the plasma prothrombin level of the baby can be raised severalfold in this way, even when the vitamin is given as late as four hours before delivery. The question at once arises, of course, as to the practical value of such a procedure. Will it diminish stillbirth and neonatal mortality by preventing a certain number of deaths from cerebral bleeding? It is realized, of course, that massive cerebral hemorrhage, resulting from severe birth trauma, cannot be prevented by this measure; but it must be remembered that the most common site of cerebral hemorrhage in the newborn is subtentorial, that is, within a small, confined space near the vital centers where a minute hemorrhage may be fatal. To date, Hellman and Shettles have administered vitamin K to more than 500 expectant mothers and are finding that this prophylactic procedure definitely reduces the incidence of all types of hemorrhage in the newborn. Details of the study will appear in an early issue of this JOURNAL.

APNEA NEONATORUM

NICHOLSON J. EASTMAN, M.D., BALTIMORE, MD.

TERMINOLOGY

ALTHOUGH questions of nomenclature are usually of academic interest only, occasionally a term is encountered which is so inept that it leads to incorrect thinking and an erroneous concept of the condition designated. Deeply entrenched as "asphyxia neonatorum" is in obstetric terminology, there is reason to believe that it belongs in this unhappy category.

Few words have undergone such radical changes in meaning as *asphyxia*. The term comes from the Greek *ἀσφυξία* (*â*, not + *σφύζειν*, to throb) and means literally absence of pulsation. It was used in this sense by Galen to describe the state of an artery distal to a tourniquet and, as late as the eighteenth century, seems to have carried no other meaning. Thus, in 1706 Phillips described asphyxia as "a cessation of the pulse throughout the whole body; which is the highest degree of Swooning and next to Death"; while Quincy in his *New Medical Dictionary*, published in 1730, defined the term as a "deficiency or privation of the pulse in some cases where it stops for a time." By 1778 the word was being used in a broader sense to convey the idea of apparent death, as from drowning, and in that year an essay by T. Brandt carried the title, "The Cure of Asphyxia, or Apparent Death by Drowning." In a later edition of Quincy's dictionary published in 1794, the earlier definition is entirely deleted and in its place we read that asphyxia "happens from a long failure of vital and animal power, as from drowning." With the beginning of the nineteenth century the import of the word centered more and more on the suffocation which results from drowning, and at the same time its connotation became extended to include suffocation from other causes, such as strangulation and noxious gases. This meaning, of course, has persisted to the present; but when it is recalled that the pulse in asphyxiated animals continues to beat long after all signs of respiratory action have ceased, it becomes apparent that our word *asphyxia* represents a most curious infelicity of etymology.

From a practical viewpoint a much more important objection to the term is the fact that obstetricians have taken further liberties with it and customarily refer to any baby who does not breathe at birth as "asphyxiated," whether the cause be lack of oxygen, cerebral hemorrhage, congenital defect or whatnot. This use of one etiologic condition to denote the whole syndrome of apnea at birth, from whatever cause, is not only illogical but slights some of the most important etiologic factors. It ignores entirely the gravest cause of apnea, birth trauma, as well as the commonest cause of *temporary* apnea in modern practice, namely, narcosis. Moreover, by focusing attention solely on

not permit marshaling the huge mass of factual data bearing on this question, but anyone familiar with recent statistical studies of the problem will find this conclusion inescapable. Respiration in the premature baby is at best a precarious business and should not be hampered, in our opinion, by depressant drugs. Turning now to possible beneficial effects conferred on the infant by analgesics, there is a growing conviction on the part of experienced observers that the necessity for difficult midforceps operations arises less frequently in patients who have been given sedation. This is ascribed to the fact that such women enjoy more rest throughout labor and are sometimes better able to rotate the head and bring it to the perineum than a patient exhausted by pain and loss of sleep; such women, moreover, are less likely to suffer from premature operative interference since they are not crying constantly with pain; in other words, the obstetrician is more disposed to give the patient additional time. Whatever the explanation may be, several clinics, including our own, report a diminished incidence of midforceps in this group.

Anoxia.—If oxygen determinations are done on the umbilical vein blood at birth, it will be found that most apneic babies (narcosis cases excluded) show very low oxygen levels. This anoxia may be the primary and determining cause of the apnea, as in prolapse of the umbilical cord, for instance; or it may be secondary to cerebral hemorrhage and a number of other conditions which interfere with the fetal circulation and thus prevent proper oxygenation of the blood in the placenta. Since, conversely, anoxia is a common cause of small cerebral hemorrhage, the situation is avowedly a complicated one and it is often difficult to determine positively the primary cause of the apnea in a given case. However this may be, from a practical viewpoint, the most important thing to bear in mind is that most apneic babies *are anoxic*; as we shall see presently, this is the dominant consideration in the treatment of the condition.

Prematurity and Congenital Malformations.—Although prematurity is the most common cause of neonatal death, it is seldom responsible for actual apnea at birth unless narcosis or cerebral hemorrhage is superimposed. Similarly, congenital malformations are a more common cause of early neonatal death than of apnea neonatorum.

TREATMENT

In the presence of anoxia, apnea is resistant to all types of treatment other than correction of the anoxia itself. In a recent study of experimental anoxia by Kreiselman and myself, even convulsive doses of alpha-lobeline, metrazol and coramine, whether injected intravenously or directly into the carotid artery, were found to have no effect whatsoever on anoxic apnea; on the other hand, a few insufflations with oxygen produced immediate breathing. In other words, there is only one way in which respiration can be initiated when suppressed by anoxia and that is by the administration of oxygen. It is our opinion, therefore, that insufflation with 100 per cent oxygen transcends all else in the treatment of apnea at birth. Attempts to stimulate respira-

Narcosis.—As we have indicated, the commonest cause of *temporary apnea neonatorum* is anesthesia and analgesia. In my experience, nitrous oxide oxygen pushed (without ether) to the point of surgical anesthesia is a more frequent offender than realized, because of the resultant fetal anoxia. The time element here is most important, and pure nitrous oxide, administered for four to five breaths to produce analgesia, probably causes less anoxia than a mixture of 85:15 continued for five minutes. So far as operative obstetrics is concerned, it seems plain that when nitrous oxide oxygen is given in concentrations of 90:10 or stronger over periods which exceed five minutes, marked degrees of anoxia are produced in about one baby out of every three. The anoxia may not prove harmful, it is true, but in an occasional case it may be associated with profound and even fatal apnea. An adequate saturation of the fetal blood with oxygen can be guaranteed only if the mother receives fifteen parts of oxygen to every 100 parts of the gas mixture, and to satisfy this end, ether should be added to the gas mixture if the latter, in proportions of 85:15, does not suffice. After prolonged labors, in particular, babies seem to withstand anoxemia poorly, and if an operation is necessary in such cases, we prefer ether on an open mask to insure liberal oxygenation of the child's blood. The same is true of breech extractions in which there is an inherent tendency to fetal anoxia due to the impingement of the child's shoulders and head on the umbilical cord.

Since ether passes readily through the placenta, it naturally exerts an anesthetic effect upon the child, and it is this influence apparently, and not anoxia, which causes the occasional "etherized" baby to be slow in breathing. Provided there is no cerebral injury, however, we find that these babies react well to time and gentle stimulation. Certainly, in our opinion, their prognosis is immeasurably better than those in which the apnea is the result of profound anoxia.

We now come to one of the most controversial questions in modern obstetrics, namely: Does the apnea of the newborn which commonly follows the use of modern analgesic programs (barbiturates, paraldehyde, scopolamine, etc.) so jeopardize the baby as to condemn the employment of these drugs? Beyond question, these sedatives, given in amnesic doses, do inhibit the onset of respiration in 40 to 60 per cent of cases, the duration of the apnea varying from a few seconds to half a minute, as a rule. Expediency, moreover, very often dictates the use of outlet forceps in these cases, so that inhalation anesthesia to the surgical degree is superimposed on the drug action, with well-known synergistic effects. If modern analgesia is to be evaluated on the basis of sound obstetrics (dismissing for the time being humanitarian considerations), the following two questions must be answered: Are the babies *permanently* harmed by the temporary apnea? Do any advantages accrue to the baby as the result of such analgesia? Obviously, the first question can best be answered in terms of actual results, that is, by statistics. It is my impression, based on available reports as well as on my own material, that the ultimate outcome for the baby born under analgesia, intelligently administered, is just as good as for one born under no analgesia, provided the infant is mature. Space does

CONTRACEPTIVE PRACTICES

GEORGE W. KOSMAK, M.D., NEW YORK, N. Y.

ALTHOUGH acknowledged for centuries, the practice of contraception has assumed a different aspect during the past quarter of a century. One of the most signal changes is the acknowledgment of the responsibility of the medical profession in the application of proper and adequate contraceptive measures and their indications. A review of progress, if we may so designate the changes in ideas and technique, is beyond the intentions of this brief article, but attention may be called to the appreciation which has developed in more recent years for the need of controlling and perhaps limiting human fertility under certain definite indications. The indiscriminate, unrestrained, and often unreasoned propaganda of an earlier period no longer prevails. The indications, both medical and social, using the latter term in its wider implications, have been established in a more satisfactory manner, adequate scientific research of means and methods has served to demonstrate the ineffectiveness of earlier procedures, and the thought has gained ground that the physician should exercise his prerogatives in employing contraceptive methods as a part of his legitimate practice. In this connection it has come to be realized that proper concepts depend upon proper teaching and that the medical school curriculum may need to be expanded to include such instruction. However, the fact must also be stressed that control of fertility is no more important than the problem of infertility, for the natural diminution of the birth rate in the higher civilized groups has brought about a fear of depopulation with its evident consequences.

Perhaps this is no place for preachment, but one cannot escape the thought that unless this movement for the artificial control of conception is carefully guarded and regulated, it may in time manifest not only a directly harmful effect on natural population growth but tend toward a resolution by men and women not to accept their responsibilities towards childbearing. It is fortunate that the modern eugenist has come to an appreciation of the import of these questions.

Whether procreation can or should be regulated is a problem in the minds of many people; it is no longer an academic question. There is a firm conviction on the part of the public that childbearing is a matter which they want to decide as individuals. We must differentiate this from the conception by which pregnancy is regarded as merely undesired or inconvenient.

Physicians have not constituted in the past an active or influential force in guiding sane and legitimate contraceptive practice in the proper direction. They have failed to realize the importance of the movement and have done little to overcome the hysteria and exaggeration which have characterized the former agitation for "birth control"—a term

tion by adding carbon dioxide to the oxygen are not only futile (since all forms of stimulation are futile in the presence of anoxia), but may even be dangerous; the same applies to the drugs mentioned above.

The main desiderata in the treatment of apnea at birth would seem to be four in number: (1) *Warmth*. These babies are in a state of vascular collapse and should be treated as is any patient in shock. (2) *Posture*. The head should be declined about 30 degrees to favor gravity drainage of fluids in the trachea, but should not be placed so directly downward as to augment a pre-existing cerebral hemorrhage. (3) *Aspiration of mucus*. Clear air passages are essential, and mucus must be removed by means of a catheter, employing either mouth suction or an electric aspirator. (4) *Delivery of 100 per cent oxygen to the pulmonary alveoli*, by adequate apparatus such as the Kreiselman resuscitator. Mouth-to-mouth insufflation, provided it is done gently (never over 20 cm. of water pressure), is usually a satisfactory substitute.

and investigation, but much remains to be done to eliminate the unfortunate and often hysterical aspects which have characterized the movement in the past. "Birth control" in the generally accepted, popular sense, is not a panacea for the evils of this world.

A development of particular interest in recent years is the public health aspect of contraception. Both local and state organizations have given this official recognition, and clinics are supported by public or private funds. "Mothers' Conferences," "Marriage Consultation Centers," and similar euphonious terms are employed to overcome possible prejudices. A recent survey lists, in 1939, a total of 166 clinics in some 20 states, in most of which, it is stated, advice is given on medical grounds only; in others economic and social circumstances suffice.

If public health departments have given careful recognition to the movement as a part of their services, it is difficult to reconcile their activities with established Federal statutes. It would seem that the time has arrived when outworn legal restrictions should be abolished or at least revised in conformity with professional standards and scientific practices.

There is a sane and an insane approach to the problem of contraception—it is to be hoped that within another decade or two, an adequate solution may be reached.

which is an unfortunate misnomer. As regards the excesses in the propaganda for the latter, I would like to repeat here what I have said on other occasions, namely that the wider employment of contraceptive measures has not brought about that unalloyed state of bliss which the earlier enthusiasts and exploiters had promised. The doctor was looked upon by them as an obstructionist when, as a matter of fact, he was merely a doubter. However, that viewpoint is changing. If contraceptive practices are properly employed in a preventive sense, in cases of maternal illness, in over-fertility (especially when associated with definite social implications), and as a possible method for spaced parenthood, then the physician and no one else should be the guiding and directing influence. If he declines to assume this function because of inherent personal objections or religious belief, that is a matter for his own conscience and for this attitude he should not be condemned.

The last twenty years disclose a gradual change in sentiment towards contraception as a legitimate responsibility of medical practice. However, much remains to be done to place it on a more definite, scientific, and social basis, with appropriate research directed to means and methods and the problem of their evaluation.

The efforts, often well meaning, but frequently misguided, which have been employed to distribute contraceptive advice to the public must, in my opinion, be largely revised in order to label them as a medical activity and to free them from the purely propaganda aspects of the movement. The latter has had its bad effects; we need not discuss them further, nor need we dilate upon the subject as it affects the private practitioner and his patients. It is in the so-called "clinics" which are accessible to the general public that reform is necessary. These have multiplied in recent years and are largely "extramural," so far as they have no connection with established hospitals and, because of diversified legislative restrictions, are operating usually without the pale of the law. Unable to secure legal recognition, they are unlicensed and therefore uncontrolled by any supervising authority except the local policeman. If such clinics are needed for the medically indigent, they should be made an essential activity of an established hospital and removed from the domain of a doubtful sentimentality or misguided propaganda.

"Contraception," unfortunately labeled "birth control" is a proper subject for medical thought and discussion, which, however, has prominent social aspects. In the near future we will have to come to practical conclusions as to the manner in which the problem must be solved and the physician must be prepared to assume his responsibilities, he must study it, he must guide it, he must not be a mere obstructionist. Even with the time and thought given to the development of adequate, harmless, and effective methods of contraception, it cannot be claimed that anything like satisfaction has been attained in this field. This may be contrary to the claims of enthusiastic propagandists and manufacturers of appliances, but it is quite true nevertheless. Recognized authorities in the research field have many accomplishments to their credit during the past twenty years and legitimate organizations and institutions have endeavored to develop a sound basis of study

etc., should be under observation for a year, making three or four visits before a final classification as to the result obtained is made. Plastic cases, such as prolapse, may require a more extended observation to determine the final result, while minor cases may be followed for a shorter time. The visits and results are recorded on an end result card which contains a summary of the case.

At the end of the period of observation the cases should be classified as successful, partially successful, or failures, and this should not be based on the anatomic result of the operation or treatment, but upon *whether the patient was cured of the complaints for which she sought relief*.

The obstetric follow-up has a somewhat different problem than the gynecologic. It is not necessary, or practical, to have the postnatal patients return for so long a period, but we can get both the mother and baby to come back for observation at monthly intervals for three months. If there is a postnatal displacement of the uterus, lacerations, or erosions of the cervix, the patient can then be referred to the gynecologic department.

Chartered accountants are universally accepted as essential in checking hospital finances, so professional statisticians are also necessary to evaluate properly not only the general mortality results of hospital care, but to study the mortality and morbidity rates of the personnel of the staff, and of the types of treatment employed in the various diseases and conditions cared for.

As it is an established custom to have a financial audit made, surely where we are dealing with human lives and health we should employ as careful methods as in the case of our dollars. This, however, is rarely done.

For the past twenty years such an accountant's audit has been made each year by professional statisticians for the Woman's Hospital, and a report rendered which is illustrated with colored graphs and the associated figures. To secure an accurate and complete audit, professional statisticians must be employed. Compiling of hospital statistics is usually delegated to a nonmedical clerk, perhaps supervised by one of the medical staff, and is of a quantitative, not a qualitative, character.

At the end of each year the statisticians have placed at their disposal the entire case histories of the discharged patients, which are studied, the facts required tabulated, and the report compiled. In the beginning it was a pioneer work, as we had to feel our way and establish rules for procedure, and make definitions in order to insure an accurate interpretation of the results. From time to time changes in these had to be made.

Some of the basic rules upon which the audit is made are as follows:

The number of cases *discharged* during the year has been made the basis for computing death rates, *not* the number of *admissions*.

Each stay in the hospital is considered as a new case for statistical purposes, on the assumption that each time a new risk is involved for the hospital staff.

An operation is credited to the surgeon performing the operation.

THE EVALUATION OF HOSPITAL STATISTICS

GEORGE GRAY WARD, M.D., F.A.C.S., F.R.C.O. & G. (HON.),
NEW YORK, N. Y.

THE first function of a hospital is the care and cure of the patient. Codman's statement that, in the past there has been no attempt to systematically fix the responsibility for the success or failure of each case treated and that in most hospitals no responsible person or department is assigned to investigate the efficiency of treatment, is a truth that makes self-evident the compulsory need of an adequate follow-up system for end result study.

Evaluation of the results of treatment cannot be based on the condition at the discharge from the hospital alone but must be determined at the end of a definite period of observation. This necessitates a properly organized system of follow-up which, since Codman's appeal, is coming more and more into use as an integral function of every Class A hospital in accordance with the requirements of the American College of Surgeons.

Still there is much room for improvement and further development in follow-up statistical study. This applies to obstetric and gynecologic patients as it does to other groups of medical and surgical illnesses. The first essential and underlying requirement in a reliable follow-up system is accurate case histories. All our deductions as to results are of value in direct proportion to the accuracy of the records. Carelessly recorded case histories are far too frequent in many hospitals and every effort should be made to simplify history taking and to secure uniformity. We have endeavored to accomplish this in the Woman's Hospital by having a printed form, which includes all the essential facts required, placed on the margin of the history sheet as a guide for the interns and residents when taking histories. To secure uniformity for comparisons, the Standard Classified Nomenclature of Disease, in use in most American hospitals, is employed.

Dictation of operative procedures made at the time instead of days or weeks later is important to insure accuracy. Surgeons' bedside notes as well as nurses' notes should be part of the record. A summary sheet at the end of the record, containing in brief all the essential facts of the case with the signature of the surgeon in charge approving the history is of great value.

Contact is made with the patient while in the hospital by the Social Service Department, which directs her to report at the follow-up clinic for a definite period of observation.

The follow-up clinic should be compulsory for each surgeon and his assistants. The success of the follow-up depends upon the fact that the surgeon who is in charge of, and who operated upon, the patient will see and examine her.

There should be definite rules for the visits to the follow-up clinic, depending upon the type of case. Simple laparotomies, hysterectomies,

There is a need to establish standards for comparison of results, and this auditing is as necessary for the leaders of the profession as it is for the rank and file.

Our experience with the employment of a professional statistician to audit our results has confirmed most positively our opinion that such a procedure is not only a great advantage in facilitating the compilation of our statistics, but is an essential warranted by the great importance of a serious problem. It has shown us that the usual methods employed by hospitals in compiling their mortality and morbidity statistics, without proper qualifications and definitions, are practically valueless for comparative purposes.

I fear our sense of surgical responsibility too often lies dormant, lulled into a peaceful slumber by the droning of tradition and the warmth of self-satisfaction. The stimulus of light is needed to awaken it, so that the "Golden Rule" may be lived up to. That light can only come from an honest auditing of our results.

I am convinced that a comprehensive accurate surgical audit, made by those who have professional statistical training, will be the means of saving many lives, much suffering, and much money.

In the event of two surgeons operating, the one who has the responsibility is credited with the operation.

Where a junior surgeon operates against his will at the direction of his senior, the responsibility for the result must rest with the senior provided the junior registers his objection.

Operation by house surgeons are always done under the supervision of an attending surgeon, and therefore are credited to the supervising surgeon.

Classification of surgical risks, as *good, fair, bad*, is taken into consideration in evaluating mortality rates of individual surgeons.

A distinction has been made between operations and operative cases, as some patients have more than one operation during a stay in the hospital.

The ratios that have been derived by measuring postoperative deaths against these two bases have been called, respectively, the "fatality of operations" and the "mortality of operative cases."

The disposition of all surgical cases discharged out of the hospital *without* operation should be accounted for in the hospital report, otherwise a hospital's low mortality rate may be due to a refusal or transfer of poor risks.

The audits submitted annually in the form of graphs and charts depict the trend each year of the cases discharged, the death rates, the total ward and private cases of each member of the Staff and of the courtesy surgeons. These are likewise detailed separately for the gynecologic and obstetric services, with notations of recoveries, morbidities and mortalities, character of wound healing, etc., in the former, and in addition the outcome of pregnancies, types of operative deliveries, complications of labor, and fetal results in the latter.

A continuing oversight and study is thus provided by which the work of the hospital and the activities of the individual members of the Staff can be evaluated from year to year.

COMMENT

The mortality and morbidity results of a hospital staff, and the percentage of successes, partial successes, and failures of certain lines of treatment are of the utmost importance in influencing the trend of our practice and therefore the health of the community. The value of these percentages must be based upon the reliability and completeness of our records.

A successful follow-up clinic depends upon the fact that the surgeon who operated, or was in charge, will examine the patient. If the patient knows that she is going to see "her doctor," she will come back for a check up, but she will not return with the same readiness if an intern or assistant is to pass judgment upon her.

These end result studies of a follow-up clinic are of great value to the patient, to the surgeon, and to the hospital. For the patient, mortality and morbidity are reduced; for the surgeon, his illusions are dispelled; and for the hospital, greater economy.

The economic value of end result study is incontrovertible. The surgeon becomes more proficient and is stimulated to greater efforts and to the correction of faults.

The days saved to the patient and to the hospital by more speedy convalescence, mean money saved to both patient and hospital.

There is the same need for auditing our surgical results as there is need of auditing our finances.

always under competent supervision by the nursing and resident staff and can attend to other duties during the earlier stages of labor with the assurance that their instructions are being observed and that the patient is not being neglected. They can call for trained assistance and special technical therapeutic agents when the need arises. They can provide excellent anesthesia of any desirable type and can safely give considerable pain relief by the use of analgesic drugs. By and large, hospital delivery is easier on the attendant, who can not only give better care to individual patients but who can give more women the advantage of his skill and experience.

The more serious dangers attached to hospital confinement are those inseparably linked with the availability of the very facilities which make it a life- and health-saving refuge. The operating room and its many instruments may have an irresistible attraction, which is further enhanced by the presence of modern anesthetic agents and trained anesthesiologists. Operative delivery is easy on the accoucheur, it saves his time, and, moreover, enables him to acquiesce with the family's demand that he "do something," and thus augments his local reputation and expands his ego. His unfortunate results are covered by alibies, the falsity of which are not realized by the relatives, who are told that everything possible was done: the baby who died of intracranial hemorrhage had "congenital heart disease," the child who died from maternal overdosing with sedatives or oxytocics had the "cord around the neck," the mother who failed to survive had "pneumonia" not puerperal sepsis, "heart disease" not shock.

Within the past few years an intelligent attack upon this problem has been made in many of the larger hospitals through the development of an organized obstetric service. Staff members are chosen from those who have had adequate special training and rules are developed and enforced, seeking to safeguard the patient. Major operative procedures cannot be done without preliminary consultation with a staff member except in grave emergencies, and members of the courtesy staff must submit to supervision of their work by those in the permanent organization. The advantages of such a system are obvious even though it attacks the rugged individualism of the physician, a hold-over from the horse-and-buggy days when the profession had not been integrated and special ability was not so highly developed. It can easily be shown that here as elsewhere in medical practice there are definite advantages in consultative discussion and in therapeutic restriction in the interest of safety.

The past ten years have shown a considerable and encouraging decrease in maternal mortality generally over the country. So many possible etiologic factors enter the picture that their individual evaluation is impossible. Better and more uniform prenatal care undoubtedly has played a major role even though it is still frequently of a sketchy and inadequate character. The organization of circuit and intramural courses of instruction has created a renewed interest in obstetric problems and has disseminated more widely the recent advances in the care of maternity patients. The improvement and enlargement of facilities

THE INCREASE IN HOSPITAL DELIVERIES

E. D. PLASS, M.D., IOWA CITY, IOWA

DURING the past two decades there has been a marked reaction against the old traditions that babies should be born at home; each year has seen an increasing percentage of hospital confinements. This tendency has been deprecated by many older practitioners who still insist that hospital delivery is not only more expensive but more dangerous, since the patient is subjected to contact with infectious agents and other influences against which she has no effective defense. So far it has been quite impossible to evaluate the claims of the rival groups; the proponents of each concept being quite irrevocably convinced of its virtues. There are, however, certain phases of the problem which may be considered with reasonable objectivity.

There can be little doubt that home delivery, reduced to its bare necessities, is less expensive than hospital confinement, and will therefore continue to be the choice of those for whom economic considerations are paramount. On the other hand, the expense of providing in the home conditions at all comparable to those available in any good hospital weighs the scales in favor of the latter. Nursing care, even by a single trained nurse, additional domestic help, medical supplies, and other incidentals undoubtedly cost more than in the hospital where everything is supplied economically on a mass basis. In the larger cities, another factor, limited and unsuitable small apartments, almost compels institutional care.

It is probably true that uncomplicated deliveries can be conducted safely at home, but when complications arise, the advantages of hospital facilities are undeniable. The major obstetric difficulties, obstructed labor, severe toxemia, hemorrhage, and obscure associated disease can only be handled adequately in a well-equipped hospital where operating equipment, dietary and laboratory facilities, transfusions, and prompt consultation are available. The development of any one of these serious complications constitutes a real argument for hospitalization.

Statements by older physicians that they have delivered three or four thousand women in their homes without a single maternal fatality and with a negligible fetal death rate do not stand close scrutiny. Either their serious cases were transferred to a hospital and the ensuing death charged to the institution, or a nearby practitioner was called in toward the end and each involved physician claims that the other should bear the responsibility. In any event, statistics still show that maternal deaths do occur in the homes and in hospitals among patients who were treated originally at home and admitted to the institution in extremis.

It must be admitted that many busy physicians, and especially the specialists, prefer or demand admission to a hospital for other and more personal reasons. They need spend less time with each patient who is

THE APPLICATION OF SCULPTURE TO PRACTICAL TEACHING IN OBSTETRICS

ROBERT LATOU DICKINSON, M.D., NEW YORK, N. Y.

FOR telling effect and minimal mental effort only three-dimensional instructions can adequately demonstrate certain bodily functions and several structural relations. Chief among these is mechanism of delivery. And herein there is every reason for combining high art of sculpture with scientific research, whether this instruction be for medical college or for popular teaching.

In 1886 I enlisted the aid of the sculptor, J. Massey Rhind, in making my scale models of the pelvis and fetal skull; made teaching models with pessaries;¹ others of the complex relations of the pelvic floor and the related organs;² and later used flexible models of perineal lacerations for students to repair.^{3, 7} Since last year that distinguished pupil of our great anatomist Huntington, the sculptor who has made so striking a contribution to anthropology for the Hall of Man in the Field Museum, Malvina Hoffman, has been counsellor in this presentation of the stages of labor. She helped secure the services of Abram Belskie, who has been willing to harness his fine talent to the slow pace of extreme exactitude in scale and finished detail in tissue.

The goal in view was a forthright change from the slumped and relaxed state of post-mortem sections heretofore copied for obstetric pictures in textbooks to the *alert upstanding tensions of the living*, as depicted in x-ray films, taken at each stage of active labor. Very special exposures are included for this series, such as those of the *ascent of the external os nearly to the inlet*, while several unpublished studies are incorporated, such as those of the thickness of the uterine wall, the location of the placenta, the projection of the forewaters, the relation of arms and legs. I am deeply in debt to the great collection at Sloane Hospital (4,800 patients); to the Obstetric Departments at Yale and Johns Hopkins; and to the studies at Beth Israel and Harlem Hospitals. Drs. Caldwell, Moloy, Thoms, Dipple, Snow, and Ball have made possible the live look of our sculptures.

For the notable thickness of the pelvic floor shown in Fig. 1, all of the full-term sections of the region, including those of Canton's great unknown Argentine atlas,⁴ were traced or drawn to full scale and then superimposed, demonstrating a striking similarity, except for two instances. The extreme thinning of that massive structure seen in Fig. 2 is the result of my study of 1882, wherein I let the advancing head mold the thinnest possible lead sheet between it and the perineum; then against the metal I could insert a puncturing needle to measure the attenuation to 4 or 2 mm.^{2, 7} The "Birth Prelude" disc on the stages of fetal growth is worked out mainly from Scammons and Calkins,⁵ and the embryology under counsel from Streeter.^{7, 8}

for training obstetric specialists and their certification by the American Board of Obstetrics and Gynecology have made expert attention more widely available. The activities of the Federal Government, through the Children's Bureau, have enabled the States and their subdivisions to provide certain facilities previously denied those in the lower economic groups. The American Committee on Maternal Welfare has worked through its state and county components to raise the character of prenatal supervision and the quality of general maternity care. Clinical and laboratory investigators have thrown new light on obstetric problems and have developed improved methods of treatment which are widely disseminated through the medical press. The public has aroused itself to the deplorable and preventable conditions which formerly prevailed and has demanded that the situation be improved. The younger, child-bearing women of the present tend to ignore the providential character of maternity and to take an intelligent interest in their reproductive careers and to demand more adequate care. Hospitals have become widely available over the nation and are being used increasingly by obstetric patients, as their facilities for adequate care improve under the stimulation of the American Medical Association, the American College of Surgeons, and other interested bodies.

It would be too arbitrary to assign relative values to any of these various factors but undoubtedly equitable to state that they have conjointly been largely responsible for the diminution of obstetric mortality. It also seems quite indisputable that the hospitals have had a considerable role in this encouraging development, depending upon the organization, ability, and conscientiousness of the attending staff. The small, inadequately equipped institution with no staff organization and no specially trained personnel probably offers no real advantages over the home and may even increase the hazard by encouraging radical and ill-advised operative deliveries and other dangerous procedures. On the other hand, the better institutions with their modern facilities, alert and progressive staffs, consultation requirements, trained supervision, and a critical attitude toward their accomplishments constitute an important factor in the provision of complete and adequate maternal care. The expansion of such facilities should further decrease the number of preventable maternal and infant deaths.

In conclusion, it may be offered that the trend toward institutional delivery is sound and its expansion inevitable, provided the hospitals continue to improve their equipment and personnel, and agree to such restrictions on individual initiative as are most conducive to the greatest safety for the mother and her child.

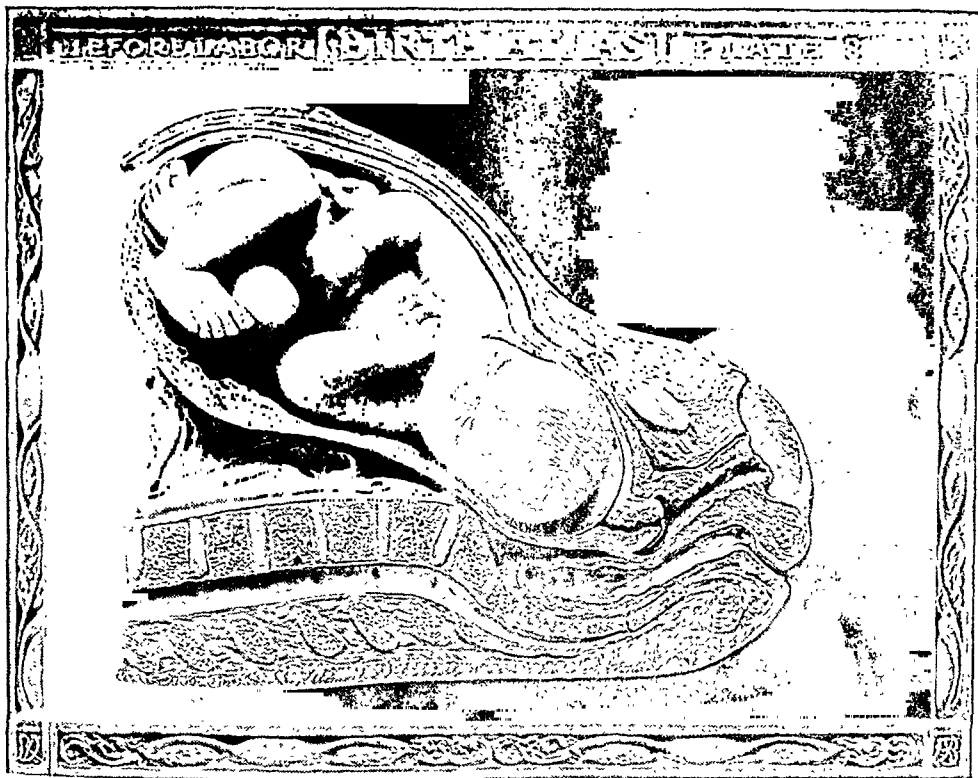
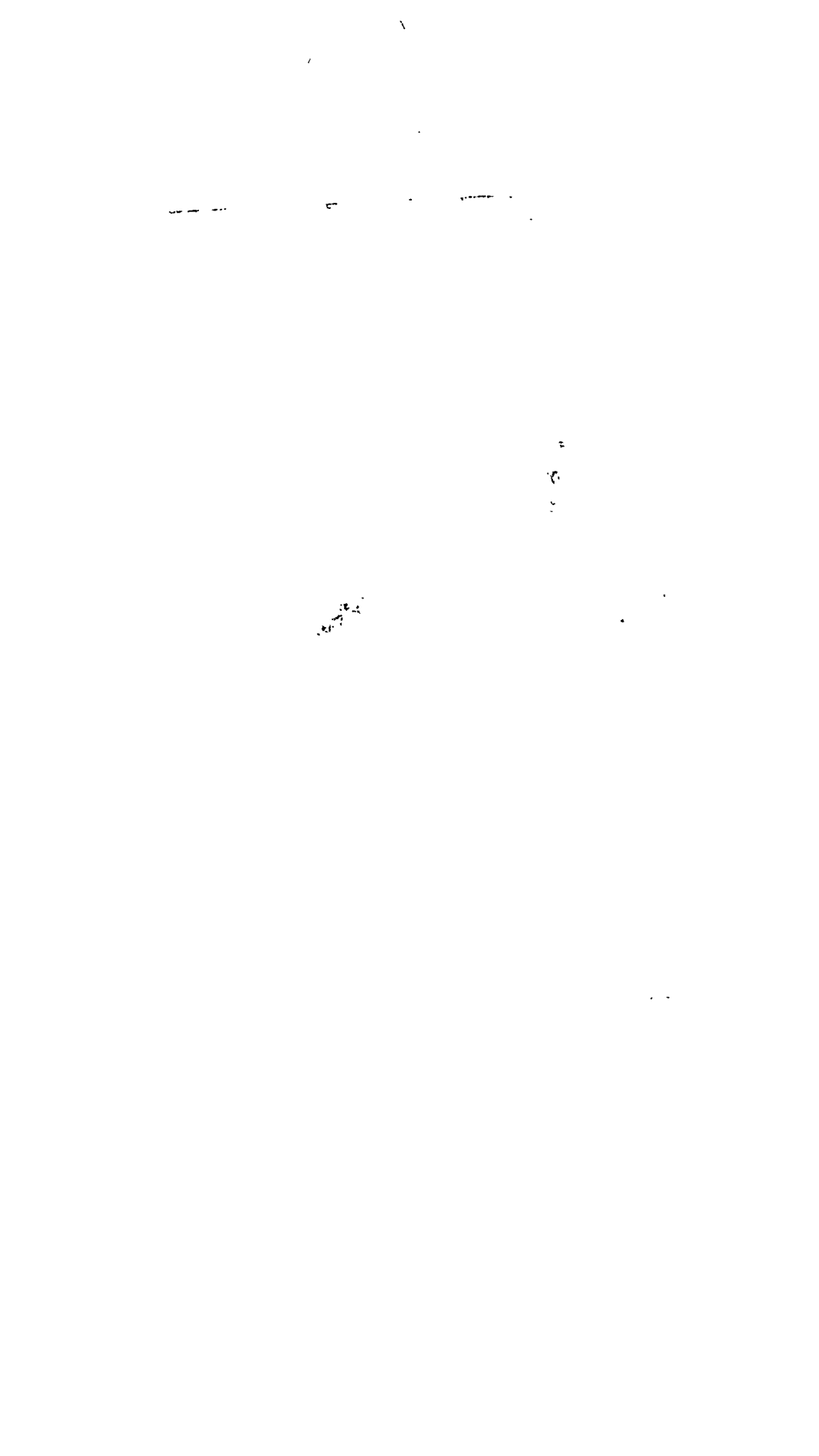


Fig. 1.—At term. Woman in median section, child in full round. Cast in terra cotta plaster from plasticine original. Thickness of pelvic floor carefully studied.



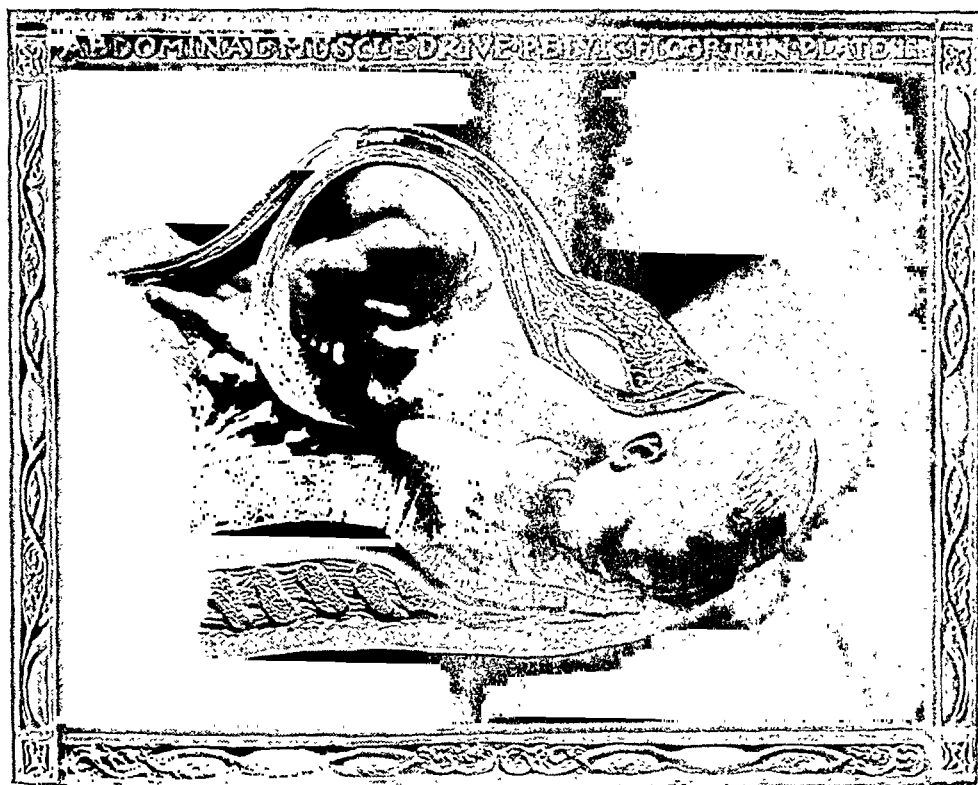


Fig. 2.—Head crowning, abdominal muscles active. Thinning of pelvic floor demonstrated.

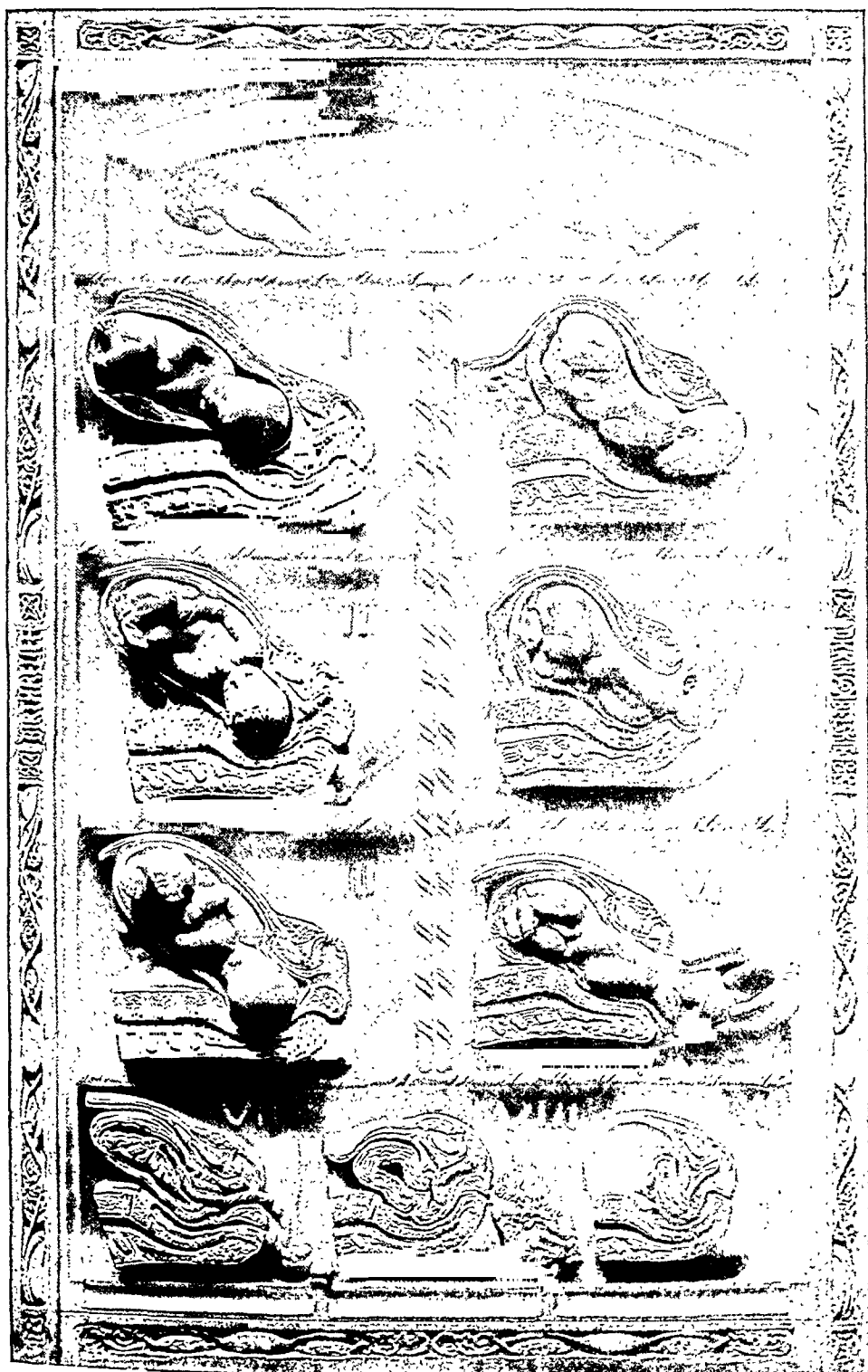


Fig. 3.—Ten-panel model of stages of labor (25 by 39 inches). Provided with box whose doors carry diagrams fully labeled, as a kind of triptych, and called Birth Relief.

obscure or spoil the illustration. Color to be used as often as is essential to understanding or good teaching quality, if cost can be met.

The best results can be gotten with that close co-operation between author and artist that is found, but is oftentimes absent. The author should always assemble all data and abstract them, such as measurements, and hunting out the best previous illustrative material. He should make sketches, even if crude, and space his lay-out. If he can make one original to set the pace, he gets what he wants across to the artist, especially in detail of anatomy, in the instance of these models, in presentation of bone or fat, uterine wall, twist of cord. To the artist he leaves beauty of form of limb and hand and foot, but, with each, provides measurements to the millimeter. The final check on dimensions and finish is the author's and he is fortunate if he can make the ultimate corrections, matching the artist's touch. For repetitious areas, such as bone or muscle, the work can be done with economy by an art student. This making of example and finish, and some full models, has been my part.

Models involve relatively high cost, compared with the best drawings, until the demand for a given series lowers the rate. The museums of natural history give to medical instruction examples of highest effectiveness with maximum attractiveness and appeal, by full-form, full-texture, full-color presentation. It will be noted also that feeling of actuality is conveyed completely only thus in the round, and to such an extent that photographs of models convey this feeling as few drawings succeed in doing.

Aided by funds from Maternity Center Association, Field Museum, National Committee on Maternal Health, and the studio facilities of the New York Academy of Medicine.

REFERENCES

- (1) *Skene, A. J. C.*: Diseases of Women, 1890. Figs. 105-111, 140, 142, 166-170.
- (2) *Dickinson, R. L.*: Am. J. Obst. & Dis. Women & Child. 22: 897, 1889. (3) *Idem*: Am. J. Obst. 56: 778, 1907. (4) *Canton, Eliseo, and Gonzales, Juan B.*: Atlas de Anatomia y de Clinica Obstetrica Clinica Normal y Pathologica, Buenos Aires, 1910.
- (5) *Scammon, R. E., and Calkins, L. A.*: Development and Growth of External Dimensions of Human Body in the Fetal Period, 1929, University of Minnesota. (6) *Dickinson, R. L.*: Human Sex Anatomy, 1933, Figs. 79, 98, also 15, 17, 45 and 142.
- (7) *Idem*: Control of Conception, ed. 2, 1939, Fig. 7, pp. 25, 30, 31, 40.

Except for the three-foot panel of stages of the ten-day trip down the Fallopian tube and some embryos, the entire presentation is of average dimensions carefully estimated by a special research. One modification, however, is the panel nearly four feet by two (Fig. 3) of 10 sections in full relief, on a scale of halved dimensions. Herein are certain noteworthy contrasts of importance: (a) that between the uterine cavity before labor and the total distended birth canal, because the models of the babies are removable; (b) that between the head imbedded and molded; and particularly (c) that between the full-term flexed fetus and its elongated sausage shape just before its exit.

The frontispiece shows the three-foot disc called "Birth Prelude," with eleven stages of growth, life size, all labeled. The spiral form was chosen for compactness and decorative quality because of the awkwardness of the usual horizontal presentations.

This initial "Birth Series" comprises 18 models in terra cotta plaster. There are 9 stages of growth, 6 steps of labor, including placental expulsion, then the empty uterus, and one stage of involution. There are nonpregnant normals of the pelvic contents in median section, and the same displayed and sectioned transversely. The embryos, in situ (and enlarged), take up weeks 4, 6, 7, 10, and 14 (menstrual age) and demonstrate also placental site and circulation.*

Applicable in principle to these and other models is the very timely plea made by Kosmak concerning the effectiveness inherent in simplicity and directness in medical illustrations. Also his warning against the prevalence of that clouding and overshadowing of essentials by detail that often obliterates the point of the picture, what he calls "landscaping" and "artistic, valueless trimmings," which I call showiness and prettiness.

The principles involved in the problem thus raised might be enumerated as follows: Use of the simplest form capable of conveying the idea. Dependence on outline alone, or diagram, whenever sufficient. Line drawing for zinc cut when rounded surfaces call for shading or tissues demand detail. For certain delicate gradations or polished surfaces, otherwise difficult to depict, drawings by brush, crayon, or stump, for halftone reproduction on coated (glazed) paper at the higher cost both of cuts and book. Where three-dimensional representation can alone adequately teach, use of models, as for steps of operation or stages of labor.

To these other requirements may be added. Thus we emphasize the following: Scale in relation to life to be a primary consideration for every photograph, drawing, or model, with invariable statement of that scale. Each series, or each set of steps, to be shown on the identical scale, and so reproduced. Labels to stand close to, or even on the part, if not defacing, or on lateral margins with connecting line. Diagrams to accompany the illustration if original is less than clear, as in very many x-rays. Also when letters or numbers or lines would

*An atlas, full size, of the models has been issued by the Maternity Center Association.

rectory of Certified Specialists, in addition to functioning as the focus for all routine matters. No one other than a Board member can fully appreciate the amount of work which devolves on each one throughout the year. All but the President are appointed to various committees: Credentials, Examination, Budget and Finance, and Graduate Training. Each one reads innumerable written examination papers and case records for many months before the oral and practical examinations are held. Although mistakes have been made, the examiners have labored faithfully, unswerved by extraneous influences, favoritism, or prejudice, and regardless of censure or applause.

Between September, 1930, and January, 1932, 255 recognized obstetricians and gynecologists were certified on application without examination. Each of these was either a Fellow of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, or the American Gynecological Society, and limited his practice to obstetrics and gynecology, or held a professorial appointment in a Grade A medical school, or was so distinguished clinically that he received the unanimous vote of all nine Board members. The future significance of certification was apparently unanticipated by many others who might have been so certified, but who failed to file an application before the lists were permanently closed.

Since 1930, the Board has examined 1,226 applicants, of whom 992 passed and 234, or 19.1 per cent, were rejected. The total number of diplomates of the Board to date, including the 255 certified without examination and 992 who successfully passed the examinations, is 1,247. The value of every certificate issued depends not only on the maintenance of high standards by the Board, but also on the character of the practice of each diplomate. The license to practice medicine indicates that its holder is competent to assume any professional responsibility which he chooses. A certificate of competency only would be a trespass on the prerogatives of the State. The Board recognizes that many general surgeons do excellent pelvic surgery, and that many practitioners are well qualified to carry on a large obstetric practice, but these men do not claim to be specialists and require nothing more than a license from the State. On the other hand, if an obstetrician or gynecologist announces himself as a specialist, his pronouncement should assure superior training, extraordinary skill, and a background of extensive clinical experience. One hundred and two formal applications for examination have thus far been rejected by the Committee on Credentials. Certification carries with it the implication of absolute specialization, and the Board has a right to expect that its diplomates will restrict their work to obstetrics and gynecology. Each can help to preserve the prestige of his certificate by forwarding to the Secretary's office specific information regarding those who fail to limit their activities. The Board is prepared at all times to revoke the certificates of those who are found to be making excursions into other fields of medicine, and has already dropped the names of six such offenders.

THE DESIGNATION OF SPECIALISTS BY THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

WALTER T. DANNREUTHER, M.D., NEW YORK, N. Y.

THE progress made in the diagnosis and treatment of various groups of illnesses has gradually impressed upon both the public and the medical profession the desirability for qualifying specialists by some recognized official body. A certificate of specialization based on training and a comprehensive personal examination can be recognized as evidence of adequate qualification, in contradistinction to the self-styled "specialist." This distinction would seem to apply with definite significance in the field to which this JOURNAL is devoted, particularly in obstetrics, in which inexpert interference with the natural progress of normal labor, with its undue increase of operative deliveries, has contributed materially to the high puerperal mortality rate.

The American Board of Obstetrics and Gynecology was conceived in the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in September, 1927, fostered by the American Gynecological Society in 1928 and by the Section of Obstetrics and Gynecology of the American Medical Association in 1929, and incorporated in 1930. The chief objectives of the Board are to elevate the plane of obstetric and gynecologic education, training, and practice, as well as to fix standards for justifiable specialization. The primary purposes were to encourage and induce potential specialists to prepare themselves thoroughly, to persuade medical schools and hospitals to provide adequate facilities for special training, and to put the stamp of approval on qualified specialists. The principal function of the Board is to conduct examinations designed to test the qualifications of voluntary candidates for certification. Whereas in some quarters the Board's motives were originally viewed with suspicion, the quiet efficiency of its operation during the past ten years has dissipated practically all of the previous antagonism. Whatever momentum the activities of the Board have gained has been due largely to its successful accomplishments. The necessity for abbreviation precludes a review of many of the details of the Board's work which would clarify all of the misconceptions which still prevail.

Each of the sponsoring organizations was and still is represented by three elected members, who are also directors and examiners. There have been two changes in personnel during the past three years. Too frequent replacements are undesirable, because previous experience is of inestimable value to an examiner. The Presidency of the Board is of no significance whatever, as the sole reason for selecting officers is for the orderly transaction of business. All nine examiners serve on exactly the same basis, except the Secretary. The scope of his duties is shown by the fact that during the past fiscal year his office handled thirty-two thousand pieces of mail and prepared the first edition of the Di-

With the passing of time, and as the Board gained experience, the necessity for changes in procedure became obvious. First, an adequate examination fee is essential for the conduct of the organization. Whereas the fee was originally fixed at fifty dollars, after ten years of operation it became necessary in 1939 to increase this to one hundred dollars. Second, when the yearly number of applicants exceeded two hundred, as it did in 1938, the custom of holding a written examination twice yearly was found to be too cumbersome, and was discontinued. Third, the large number of candidates in the past four years has made it necessary for the Board to utilize the services of nine assistant examiners during the four days of the oral and practical examinations. These were wisely provided for in the Articles of Incorporation, and care has been exercised to invite only those who hold professorial positions in Grade A medical schools.

Two radical changes will become effective on January 1, 1941, after which three years of special training in seven, instead of five years of practice, will be required before an applicant is eligible for examination, and all applicants without exception will have to file case records and take a preliminary written examination before appearing for the oral examination. As a result of the present trend toward prolonged institutional training, the Board has recently encountered several candidates who could fulfill the existing requirements for eligibility, but who had not as yet carried the responsibility for personal private patients. On the other hand, the Board feels that within the ten years of its operation, all senior and experienced obstetricians and gynecologists have had ample opportunity to apply for certification, and there is no longer any reason to make a distinction between candidates.

The achievements and progress of the Board since its creation have been such as to make its influence felt throughout the country. Prospective applicants for certification are preparing themselves more thoroughly for the practice of obstetrics and gynecology, hospitals are demanding certification for appointment to responsible staff positions, certain medical societies are favoring diplomates of the Board, and even the lay public is becoming aware of the implications of certification. That the certificate itself is gradually gaining prestige, there can be no doubt.

observations confirm the published reports of Hamilton and Wolfe. In addition, we have been interested in the work of Friedgood⁶ who observed large acidophilic granules appearing in the hypophyses of female rabbits shortly after coitus. In five androgen-injected rabbits, similar phenomena were not discovered although the animals apparently had mated. Friedgood's findings were substantiated in 3 of 5 normal animals.

While unquestioned proof of a direct inhibitory effect produced by androgens on the pituitary of the human female has not been reported, the observation of Salmon⁷ is of interest; in one castrated woman he demonstrated a precipitate decrease in the urinary gonadotropic level after androgenic therapy. Nathanson and Towne²³ also observed a fall in urinary female sex hormone levels after the administration of testosterone to female castrates.

If there is a notable inhibition of the pituitary gland as a result of the administration of androgens, we should expect to find associated alterations in the genitalia.

The presence of cyclic changes in vaginal smears from the rat makes it simple to observe genital activity in this species. Smears from a group of adult female animals in our colony were examined until the fact that they had regular cycles could be established. They were then given daily injections of testosterone propionate. After a few days all smears showed diestrus, and the animals remained in that state as long as the injections were continued. After the injections were discontinued, the cycles returned to normal. Similar results have been recorded by Browman⁸ and by Robson.^{9, 59} Robson also reported¹³ that testosterone inhibits the ability of estrogens to induce vaginal cornification in the castrated mouse. Papanicolaou^{10-12, 61} has duplicated these animal experimental findings in the human female. Vaginal smears taken from a number of women in a series which will be reported in Part II indicated a marked lowering of estrogenic activity while the patients were receiving testosterone propionate. Smears from these patients revealed an absence of cornified vaginal epithelium; they consisted only of small, darkly staining, mucified epithelial cells with comparatively large nuclei.

Conflicting reports have appeared in the literature regarding the effect of androgens on the uterus of experimental animals. Korenchevsky and others^{14-18, 66} have noted that uterine hypertrophy and ovarian activity^{19, 20, 82-88} have appeared in the rat following the administration of male sex hormone. Williams and his co-workers²¹ state, however, that testosterone tends to decrease the endometrial hyperplasia produced in castrated guinea pigs by estrogens. Engle and Smith²² found that the bleeding following the use of estrogens in the monkey could be inhibited by testosterone propionate. Leonard, Sager and Hamilton⁵⁴ observed that testosterone propionate decreased the estrus rhythm of the rabbit uterus. That androgens will delay menstruation in monkeys was demonstrated by Zuckerman³⁵ and also by Hartman.³⁶ In every instance in which we administered male sex hormone to adult rats and rabbits over long periods of time and in amounts comparable to those given therapeutically to women, the uterus was found to be inactive with a thin endometrium and small glands. At no time were phenomena suggesting estrogenic or progestational changes observed (Fig. 1).

Geist, Salmon and Gaines^{44, 65} demonstrated atrophy of the human endometrium in suction curettings obtained after injecting patients with testosterone propionate.

Original Communications

AN EVALUATION OF ANDROGENIC THERAPY IN GYNECOLOGIC PRACTICE*

JOHN W. HUFFMAN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School and the Gynecological Service of Passavant Memorial Hospital)

PART I. A REVIEW OF EXPERIMENTAL WORK WITH THE ANDROGENS IN RELATION TO THERAPY

MANY clinical and experimental reports have recently appeared regarding the action of the male sex hormone upon the female genitalia. During the past three years an attempt has been made to analyze the effects of androgens when administered to laboratory animals and to human beings. It is proposed to correlate the results of these efforts with those previously recorded in the literature. Although the outcome of experiments in the use of male sex hormone will be reported herewith, a chief motive in preparing this paper has been a desire to clarify the use of androgens in gynecologic practice.

The experimental work upon which the use of the male sex hormone in gynecology is based will be considered in Part I of this review. Clinical results obtained with androgen therapy will be reviewed in Part II.

EFFECTS OF ANDROGENS UPON THE FEMALE GENITALIA AND THE HYPOPHYSIS

Following the work of Ihrke and D'Amour² who were able to inhibit the sexual activity of female animals by the injection of extracts of bull testes, Moore and Price³ advanced the hypothesis that this inhibition was the result of a pituitary inactivation. This has been substantiated by the work of Hamilton and his co-worker.⁴ Their investigations have shown that the pituitary glands of androgen-injected rats, when transplanted into immature females of the same species, have a decreased gonadotropic activity. They⁵ have also demonstrated histologic changes in the hypophyses of female rats after repeated injections of testosterone propionate given over a prolonged period. A decrease in the number and a degranulation of the basophilic elements were evident in the pituitary glands of the animals which they injected with male sex hormone.

During the course of several recent investigations, examinations have been made of the pituitary glands of adult female rabbits, and of immature, and mature female rats which had received frequent injections of testosterone propionate† over considerable periods of time. These

*Presented at a meeting of the Chicago Gynecological Society, May 17, 1940.

†Testosterone propionate in the form of Perandren was very kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for all of the author's investigations reported herewith.

The ovaries from mature animals injected with androgenic substance show little gross or histologic deviation from the normal. There is an absence of corpora hemorrhagica or recent corpora lutea after the injections have been given for a number of days. Atretic follicles are present. The primordial follicles appear unchanged by administration of the male sex hormone. This is in accord with published reports that follicular and luteinizing changes in the ovaries of laboratory animals are prevented by injections of testosterone propionate⁷⁷ (Fig. 2). Similar observations have been made in the human being. They will be described in more detail later in this report.

The external genitalia of the mouse,⁸¹ the rat,⁶² and the rabbit exhibit marked responses to repeated injections of massive doses of testosterone propionate. In the adult female rat the phallus becomes notably hypertrophied and in several instances in our animals an os priapi was demonstrable histologically (Fig. 3). In the rabbit after the injection of large amounts of androgenic material, the

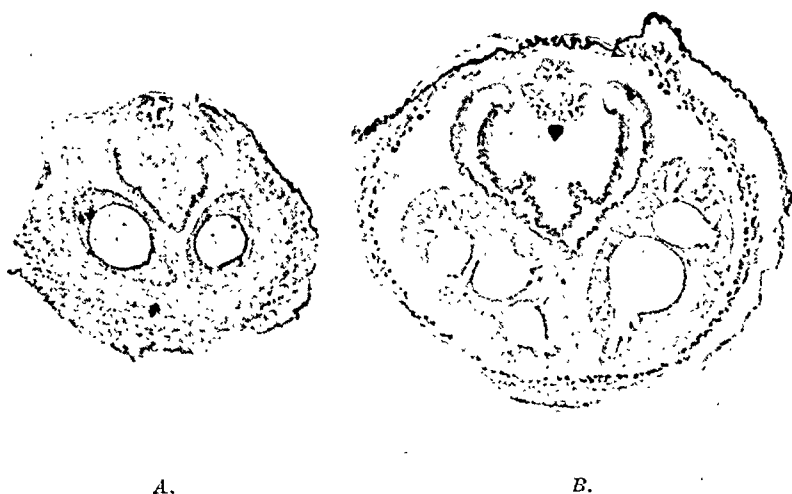


Fig. 3.—A, Photomicrograph of a section through the phallus of a normal adult female rat. B, Similar section through the phallus of a female litter mate which had received 3 mg. of testosterone propionate daily for twenty-one days. The marked hypertrophy in the latter with the appearance of an os priapi beneath the urethra is evident. Both photomicrographs $\times 10$.

penile structure at the upper margin of the vaginal orifice developed to a size comparable to the penis of the male (Fig. 4). Hamilton and Wolfe⁵⁷ have noted the development of a prostatic type of paraurethral gland in female rats after administration of male sex hormone. These changes seem to develop in proportion to the amount of the hormone administered. In those animals not destroyed after the injections were discontinued, the androgenic manifestations gradually subsided, and the genitalia returned to normal. In a certain percentage of women, comparable masculinizing changes develop, as reported by Greenhill and Freed²⁴ and by Varangot.¹ Similar results have been observed in some of the cases followed in the dispensary at Northwestern University Medical School and will be mentioned in more detail later.

Numerous reports in the literature state that luteinizing and cystic changes in the ovaries,^{25, 71, 82} stimulation of the endometrium,^{14-16, 29, 75} and proliferation of the mammary gland,^{28, 51, 52, 55, 56} occur after androgenic therapy. Most of these experiments have been conducted with immature rats as the experimental animals. The doses of the hormone used were greater than any which would compare with the amounts administered in clinical investigations. A relatively

In my cases similar effects were obtained. Most of the patients in this series suffered from functional uterine bleeding; several were proved to have endometrial hyperplasia as shown by curettings. In each instance in which the endometrium was examined histologically

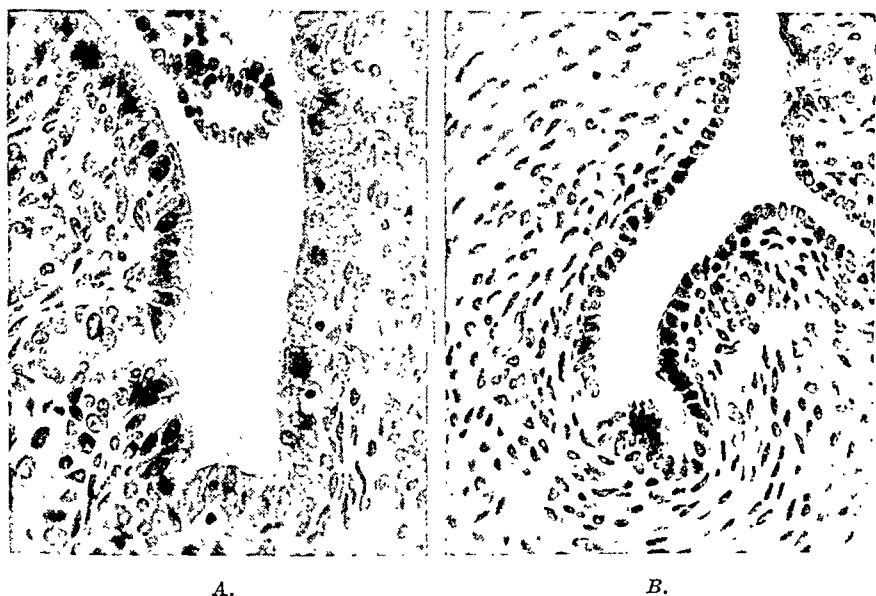


Fig. 1.—A, Photomicrograph of a portion of the endometrium in a section from the cornu of the uterus of a normal isolated adult female rabbit. B, Photomicrograph of a similar portion of the opposite uterine cornu of the same animal after it had received 2.5 mg. of testosterone propionate every other day for thirty-six days. Thinning of the endometrium and lessening of cellular activity in the latter is evident. Both photomicrographs $\times 660$.

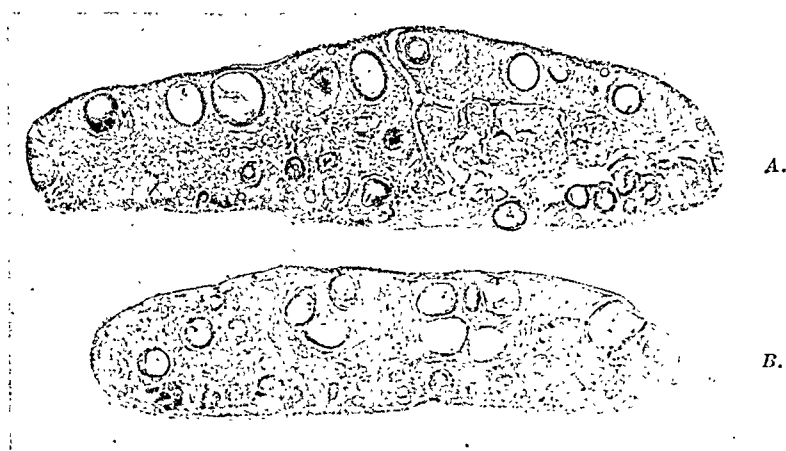


Fig. 2.—A, Photograph of a longitudinal section through the right ovary of a normal adult rabbit. B, Similar section through the left ovary removed after the animal had received 2.5 mg. of testosterone propionate every other day for thirty-six days. The absence of any notable difference in the two ovaries is to be noted. Both photographs $\times 11$.

after patients had received 250 mg. or more of testosterone propionate, it was observed that the endometrial glands were small and far apart. They were usually lined by columnar epithelium with basal nuclei. This is a picture of inactivity rather than a resemblance of senile atrophy (Fig. 6).

Soskin³² is of great interest, as is also the suggestion of Nelson and Gallagher,²⁵ and of Mazer and Mazer that coincident with the beginning of pituitary inhibition there is a pouring out of stored gonadotropic material from the hypophysis. Either of these hypotheses might explain the apparent stimulating action of testosterone upon the genitalia occasionally observed.

THE OVARIAN RESPONSE TO GONADOTROPIC SUBSTANCE FOLLOWING PROLONGED ADMINISTRATION OF TESTOSTERONE PROPIONATE

The effect of testosterone propionate in inhibiting the cyclic phenomena in the female genitalia^{35, 36} and in producing those changes just described suggested the importance of conducting additional investigations as to its mode of action on the female genitalia. It seemed worth while to determine whether the action of this androgen was a direct one upon the ovary, or whether it was secondary to hypophyseal inhibition as strongly suggested by the work of Hamilton and of others.^{37, 63} In previously reported experiments³⁸ isolated adult female rabbits were first proved able to respond to gonadotropic substance. Following this they were given injections of testosterone propionate over a period of several weeks. The presence of corpora hemorrhagica and recent corpora lutea, as a response to a second dose of gonadotropic material administered with the last injection of testosterone propionate, was strong evidence that androgens do not inhibit ovarian activity *per se*. Their action in stopping the genital cycle was, therefore, apparently an hypophyseal effect.

THE EFFECT OF TESTOSTERONE PROPIONATE UPON FEMALE REPRODUCTION*

The preceding investigations indicated that the androgens were potent agents in temporarily changing those cyclic factors in the mammalian female which have to do with reproduction. All of the experimental work thus far had pointed to the fact that the androgenic effect on the sexual mechanism was maintained only a short time after the injections were stopped. So far as was known no one had applied the critical test of attempted reproduction following prolonged androgenic therapy although the results obtained by Scipiades²⁶ and by Magistris⁶⁷ were suggestive.

Adult female rats received daily injections of testosterone propionate until it was shown by vaginal smears that they were in diestrus. They were then caged with healthy males. The daily injections of testosterone propionate were continued. As long as this procedure was followed, estrus did not occur and no young were born. The males were then withdrawn and the injections stopped; estrus recurred. After regularity of the sexual cycle was proved, the animals were again mated. Almost invariably pregnancy occurred; normal grossly healthy young were delivered.

EFFECT OF TESTOSTERONE PROPIONATE UPON LACTATION*

Reports in the literature have been made stating that in experimental nonlactating animals fibrosis occurs in the stroma of the mammary

*This item will be more fully detailed in subsequent accounts.

small number of large injections were given. I have seen bizarre effects in immature rats when unusually large doses of testosterone propionate were repeated over a short period of time. Without further study, I am not satisfied that these phenomena are estrogen-like or stimulative. Mazer and Mazer,³¹ however, found that prolonged androgenic treatment in the rat resulted in a decrease in

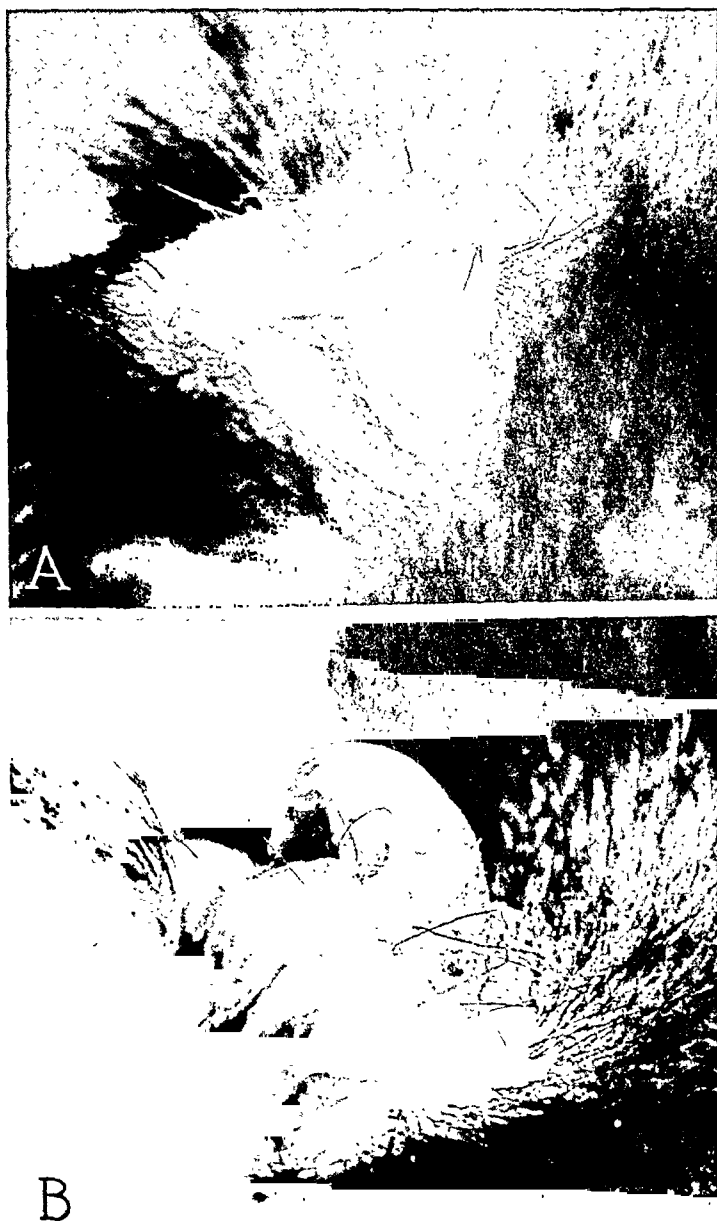


Fig. 4.—A, The external genitalia of an adult female rabbit. The vaginal aperture and slight clitoridal prominence are to be observed. B, Photograph of the external genitalia of a female litter mate after it had received 10 mg. of testosterone propionate daily for fourteen days. The great enlargement of the clitoris is evident. Camera distance for both photographs is the same.

the weights of the ovaries and uteri. They felt, therefore, that the duration of treatment is an important factor in the response of the genitalia to testosterone propionate. Hertz and Meyers⁶⁰ have demonstrated the effectiveness of small doses of male sex hormone. The biphasic action of the androgens as an explanation of their apparent gonadotropic effect, as suggested by Freed, Greenhill, and

as a result of pituitary rather than of ovarian inactivation, (3) inhibition of lactation, (4) the occurrence of temporary masculinizing characteristics after the administration of large doses of the androgens, (5) recurrence of all genital physiologic processes including normal reproduction after the administration of the androgenic substance is discontinued.

PART II. A CRITICAL REVIEW OF CLINICAL RESULTS OBTAINED WITH ANDROGENIC THERAPY

In Part I of this review the experimental studies upon which the use of male sex hormone in gynecologic practice is based were discussed. Part II, presented herewith, is a summary of clinical results obtained with androgen therapy in gynecology, with a review of the corollary literature.

USE OF MALE SEX HORMONE IN CASES OF FUNCTIONAL UTERINE BLEEDING

During the past two and one-half years records have been kept of 22 women with a clinical diagnosis of functional bleeding who received androgenic therapy either alone or in combination with other non-surgical treatment. In this group it was possible, without exception, to inhibit functional flow and menstruation when 25 mg. of testosterone propionate in the form of perandren (Ciba) were administered every other day. It usually required 10 to 15 injections (a total of 250 to 450 mg.) to stop the bleeding. Smaller doses (10 mg. twice weekly) when administered to women complaining of heavy or somewhat prolonged menstruation usually decreased the amount of bleeding and shortened the duration of flow but did not inhibit the cycle. When using the large (25 mg.) dosages, it has been customary to give not more than 2 or 3 injections after the flow has ceased. The longest period of amenorrhea following one series of injections has been one hundred and three days.

Of particular interest in this group of 22 women are three patients who have been under observation for two years or longer. Each one of these three, prior to the beginning of treatment, had bled for more than sixty days and had lost enough blood to develop marked secondary anemia. Curettage in all three had demonstrated endometrial hyperplasia. One patient, in fact, had been curetted six times between the ages of sixteen and twenty-four years. Two of them had received large amounts of anterior pituitary-like substance without benefit. All three were comely young women under the age of 35 who met the public daily and whose livelihood depended upon their continuing at work. They were all exceedingly anxious to preserve whatever childbearing ability they possessed. Androgenic therapy was begun in the form of 25 mg. of testosterone propionate injected intramuscularly every other day. In each instance the bleeding continued unabated for ten to fourteen days, after which the flow gradually ceased and stopped entirely on the twelfth to the eighteenth day. Three additional injections were given. The subsequent amenorrhea persisted for 68, 74, and 93 days, re-

gland after injections of synthetic male hormone.^{39, 70} Folley and Kon⁶⁴ and others⁸⁰ state that androgens will inhibit lactation. Robson⁵⁰ and Burrows⁷⁴ have produced evidence to show that young rats die when their mothers are injected with androgenic material. Kurzrok and O'Connell⁴⁰ and others^{70, 72, 73} have conducted clinical investigations which indicate that the administration of testosterone propionate to women in the puerperium decreased breast engorgement and pain. Numerous papers have been written regarding the efficacy of the male sex hormone in the treatment of mastalgia and mastitis.^{27, 30, 68, 69} It was therefore suggested that androgens tend to decrease breast activity. It seemed desirable to determine what effect, if any, the male hormone would have upon the histology of the breast if the young were permitted to suckle during the time the mother was receiving androgenic substance. Normal female rats which had borne healthy litters were selected. Injections of testosterone propionate were begun within twenty-four hours of delivery and continued daily. The appearance of the breasts and the state of nutrition of the offspring were observed. Histologic studies of the breast tissue were made at varying intervals of time in the puerperium. In every instance in which the mother received testosterone propionate the young died within sixteen days of birth, evidently of malnutrition. Breast tissue removed at the time of the death of the litter showed absence of lactation. Controls, injected with comparable amounts of the vehicle (sesame oil), reared healthy litters. Breast tissue removed from the controls demonstrated normal lactation.

THE REPRODUCTIVE ABILITY OF THE OFFSPRING OF FEMALE ANIMALS
PREVIOUSLY TREATED WITH TESTOSTERONE PROPIONATE*

Ivy and Greene⁴¹ have shown that injections of androgens in pregnant rats will result in grave abnormalities in the genitalia of the offspring. We have shown that females who received male sex hormone could bear grossly normal young following cessation of the injections. These progeny were followed during development. Body growth appeared normal. Records were kept of each individual and matings were made between males and females born of mothers which had received testosterone propionate prior to their pregnancies. In every instance healthy litters were obtained from this second generation. The females suckled their young normally, and the progeny developed in a satisfactory fashion.

SUMMARY

Although there is not a unanimity of opinion regarding the effects of androgenic substances when administered to female mammals, it would appear that most of the experimental work presented to date indicates the following changes develop in laboratory animals after the administration of male sex hormone: (1) A decrease in the gonadotropic activity of the hypophysis, (2) cessation of genital cyclic phenomena

*This item, herewith presented as a preliminary report, will be more fully detailed in subsequent accounts.

†Experiments on this phase of the work were conducted with Florence K. Huffman.

THE USE OF MALE SEX HORMONE IN CASES OF DYSMENORRHEA, AFTER-PAINS, AND PREMENSTRUAL MOLIMEN

In 1937, Demarest and Capitain³⁰ reported excellent results in the treatment of dysmenorrhea with injections of testosterone. Salmon, Geist, and Walters⁵³ administered testosterone propionate in dosages of 10 to 50 mg. to 30 women who complained of severe dysmenorrhea. The injections were given three times a week during the cycle. Good results were obtained in 26 of 30 patients. They felt that 250 to 300 mg. of testosterone propionate, given in divided doses through one menstrual cycle, would give relief to most of their patients. If discomfort recurred the next month, they repeated a series of injections but reduced the dosage to one-half that previously given. Greenhill and Freed^{58, 52} observed that one-half of their cases of dysmenorrhea, treated with 25 to 50 mg. of testosterone propionate given three times a week for each of the two weeks prior to menstruation, continued to have benefit one year after discontinuance of the therapy. They feel that male sex hormone in amounts less than required to stop uterine flow will relieve dysmenorrhea. Rubenstein and Abarbanel⁴⁹ found that most of their cases of essential dysmenorrhea responded satisfactorily to male sex hormone. They explained that this resulted from a lowering of estrogenic and gonadotropic levels and a consequent decrease in painful uterine contractions. Recently Abarbanel⁹¹ has found the percutaneous route satisfactory for administering androgenic substance to patients with painful menses. He prefers to use testosterone propionate in sesame oil rather than an ointment.

Premenstrual tension and major menstrual molimen were relieved by small doses of testosterone according to Greenblatt.⁹⁰ In several patients who complained of severe molimen he was able to give complete comfort and also to relieve associated excessive cyclic bleeding when he administered 10 to 50 mg. of testosterone propionate per month. Abarbanel and Rubenstein⁴⁹ have made similar observations. Abarbanel has also⁷⁰ reported that in 82 per cent of 49 patients afterpains were relieved by the injection of 10 mg. of testosterone propionate. No afterpains occurred in 88 of 100 women who received 10 mg. of androgenic substance given prophylactically at or near the time of delivery.

USE OF MALE SEX HORMONE IN CASES OF FEMALE MENOPAUSAL DISTURBANCES

Mocquot and Moricard⁴⁷ first reported the use of androgenic substances in the treatment of climacteric disturbances following bilateral ovariectomy. Margeil and Zwilling⁴⁸ found male sex hormone effective in the management of the natural menopause. These authors used very small doses without uniform results. Salmon, in 1937, reported cessation of menopausal symptoms in one female castrate following the administration of 400 mg. of testosterone propionate in divided doses. Binberg, Kurzrok and Livingston³⁴ noted the disappearance of severe climacteric symptoms which had followed castration, x-ray, and radium when they injected 10 mg. of testosterone propionate twice weekly. Subsequently they reported⁴⁶ a series of 21 patients who were relieved of menopausal headaches, flushes, and sweats by the injection of 30 to 50 mg. of testosterone propionate weekly. They began their treatment with 25 mg. twice a week, later reducing the dosage to 30 or 40 mg. given weekly. There were no failures in their cases, and they were able to administer testosterone to some women who could not tolerate estrogens. They feel there is a definite place for androgenic therapy in the management of the menopause.

USE OF MALE SEX HORMONE FOR THE INHIBITION OF LACTATION, IN CASES OF BREAST ENGORGEMENT, AND IN MASTOPATHIES

Considerable experimental evidence exists to indicate that androgens should decrease mammary gland activity. Clinical experiences bear this out.

spectively. In each case this was followed by a scanty flow of from one to three days. Three to five weeks later a slightly heavier period occurred. One month following this last flow two of the women menstruated normally, and the third had a recurrence of persistent functional bleeding requiring the repetition of a series of injections. The two who had menstruated normally subsequently noted a gradual increase in the duration and heaviness of their menses and received testosterone propionate in the dosages previously described. Series of injections have had to be repeated in all three approximately every four to six months. At no time have their blood counts fallen below normal limits, nor have they been prevented from working because of excessive flow. The other patients in this series, who have been under observation less than two years and received larger dosages, have responded in a somewhat similar manner, with the exception of two whose menstrual cycles returned to normal and have remained so for six months. No notable masculinizing symptoms have occurred in this group, except for occasional enlargement of the clitoris toward the end of the series of injections. One woman who possessed rather marked facial hair noted that it became darker; upon cessation of the treatment this disappeared.

Male sex hormone has been used more for the treatment of functional uterine bleeding than for any other gynecologic condition.

Gaines, Salmon and Geist⁶⁵ pointed out that 25 to 100 mg. of testosterone propionate injected intramuscularly every two or three days until a total of 175 to 800 mg. was given would result in a disappearance of the secretory phase of the endometrium and in an inhibition of endometrial proliferation. This they suggested was the result of suppression of the gonadotropic activity of the hypophysis. Shortly after this report, they⁴⁴ published a record of 25 women suffering from functional uterine bleeding. Twenty-four of the women were relieved by the use of testosterone propionate in doses of 300 to 1,000 mg. per month. Foss³³ not only inhibited uterine flow but produced an atrophy of the endometrium following the injection of 300 to 2,000 mg. of male sex hormone to each of 16 patients. Loeser⁴⁵ recommended a dosage of 50 mg. of testosterone propionate injected every other day with an average total monthly dosage of 500 mg. for menorrhagia. He found that with these amounts atrophy of the endometrium, inhibition of uterine bleeding, and decrease in the size of uterine fibromyomas occurred. Mazer and Mazer,⁴² Greenhill and Freed,⁵⁸ and others have reported the effective control of excessive uterine bleeding by the injection of male sex hormones. Rubenstein⁷⁷ reports one case in which the bleeding ceased after the administration of 5 mg. of testosterone propionate injected twice weekly. Sturgis and his co-workers⁷⁸ found that the minimum dosage required to lessen the flow in cases of metromenorrhagia was 10 to 30 mg. and that the total amount required to stop the flow was 10 to 120 mg. These are, by far, the smallest dosages recommended. Mazer and Mazer, Greenhill and Freed, Geist and his associates have all apparently arrived at about the same dosage as that used in the patients described in the preceding paragraphs, i.e., 250 to 500 mg. monthly, given in divided doses throughout the month. Salmon and his co-workers⁵³ noted that masculinization tended to develop when more than 500 mg. of testosterone propionate were administered, and they feel that this amount should be considered a human "threshold." Many investigators who have given androgens a clinical trial would undoubtedly prefer not to give more than 350 to 400 mg. in any one month. Most functional bleeding cases will respond to 25 mg. given intramuscularly every other day for a total of 12 to 16 injections (300 to 400 mg.). Loeser⁵⁹ has recently reported the satisfactory use of pellets of androgenic substance planted subcutaneously in women suffering from functional uterine bleeding and mastopathies.

injections, this hypertrophy disappeared. In each instance in which vaginal smears were taken after 250 mg. of male sex hormone had been given, there was an almost complete absence of any demonstrable estrogenic activity. In those instances in which endometrial hyperplasia had been observed in curetings obtained prior to treatment, it was noted that, after androgenic therapy, the tissue removed by suction curettage showed no hyperplasia; there were, instead, comparatively few, small, inactive glands (Fig. 6). While none of the patients who have been followed in this series have attempted pregnancy, Mazer and Mazer⁴² report four women from their group of 38 who had normal gestations after androgenic therapy.

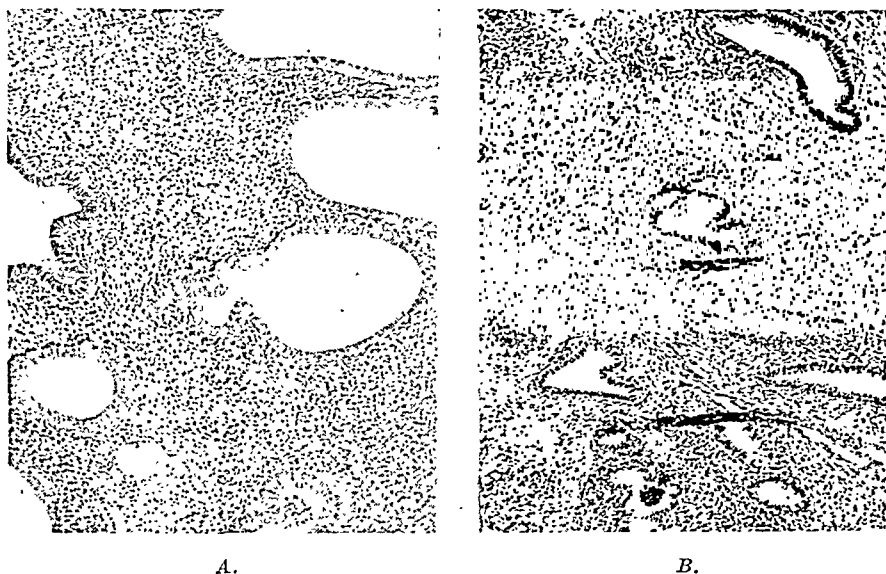


Fig. 6.—A, Photomicrograph of uterine scrapings from a patient with typical endometrial hyperplasia. She had been bleeding for seventy-two days. B, Endometrial suction curetting from the same patient after she had received 350 mg. of testosterone propionate. Both photomicrographs $\times 132$.

In one patient in whom the diagnosis of submucous fibromyomas was made and who had bled constantly for many weeks (entering the hospital with a hemoglobin of 4.5 Gm. and an erythrocyte count of 2,500,000 per c.mm.), androgenic therapy was given to inhibit, if possible, further flow during the days in which preparation for operation was being made. She received 25 mg. of testosterone propionate daily for fourteen days. It is interesting to relate that no bleeding occurred during the two weeks preceding surgery and that the transfused blood given her was conserved so that at the time of her hysterectomy she had essentially normal blood counts. Some hypertrophy of the clitoris and an inactive vaginal smear were noted the day before operation. It was felt that an unusual opportunity presented itself for observation of the gross and microscopic appearance of the genitalia in this patient who had received an average amount of androgenic therapy. At operation it was noted that the ovaries were somewhat shrunken, pale, with no gross follicles and no evident corpora lutea. The uterus, although

Demarest and Capitain³⁰ were the first to report satisfactory results when androgenic substances were administered to women complaining of premenstrual breast engorgement and mastalgias. They used small dosages (5 mg.) and did not have uniform results, probably because of the small amount of the hormone administered. Kurzrok and O'Connell⁴⁰ successfully inhibited lactation in 19 of 21 puerperal women when 25 mg. of testosterone propionate were injected intramuscularly twice daily for one to three days. None of these patients had notable engorgement on this regimen. Abarbanel⁷⁰ was able to relieve postpartum breast engorgement in 44 of 50 patients by the intramuscular injection of 5 mg. of testosterone propionate; occasionally it was necessary to repeat this dose in one hour. More recently Siegler and Silverstein⁷² and Binberg, Kurzrok and Klor⁷³ have reported inhibition of lactation following the administration of androgenic substances. Siegler and Silverstein found that injections of from



Fig. 5.—A, The external genitalia of a patient under treatment for functional uterine bleeding who had received 350 mg. of testosterone propionate given over a period of several weeks, preceding the taking of this photograph. Note the increase in the length and diameter of the clitoris with the massive enlargement of the glans. B, One month after the last injection of testosterone. Note that the clitoris is normal in appearance and that the temporary hypertrophy seen in A has disappeared. The camera distance for both photographs is identical.

3 to 10 mg. of testosterone propionate were effective in 94 per cent of their patients. Binberg and his associates injected 120 to 150 mg. of testosterone propionate intramuscularly in divided doses on the day of delivery. They record that 49 of their 56 patients did not lactate as a result of this procedure.

CORRELATION OF LABORATORY AND CLINICAL FINDINGS

In order to correlate, if possible, the laboratory findings with the clinical investigations, changes were sought for in my patients analogous to those noted in experimental animals. The discovery that comparable phenomena (as far as the investigations could be extended) did occur is of great interest.

The women who received the largest amounts of testosterone (400 mg. or more) over the longest period of time tended to develop definite hypertrophy of the clitoris (Fig. 5). On cessation of each series of

with curettings obtained in previous studies. There was thinning of the endometrium with very few glands in a nonsecretory state. These glands were lined by a single layer of cells with small basal nuclei. This is not the picture commonly seen in senile atrophy. It is rather one of inactivity (Fig. 7).

Section through an ovary disclosed small atretic follicles and no young corpora lutea (Fig. 8). The follicles were lined with small shrunken granulosa cells. There was a thin cortex containing occasional primordial follicles but no ripening or maturing Graafian follicles were found (Fig. 9). The granulosa cell layers of all follicles

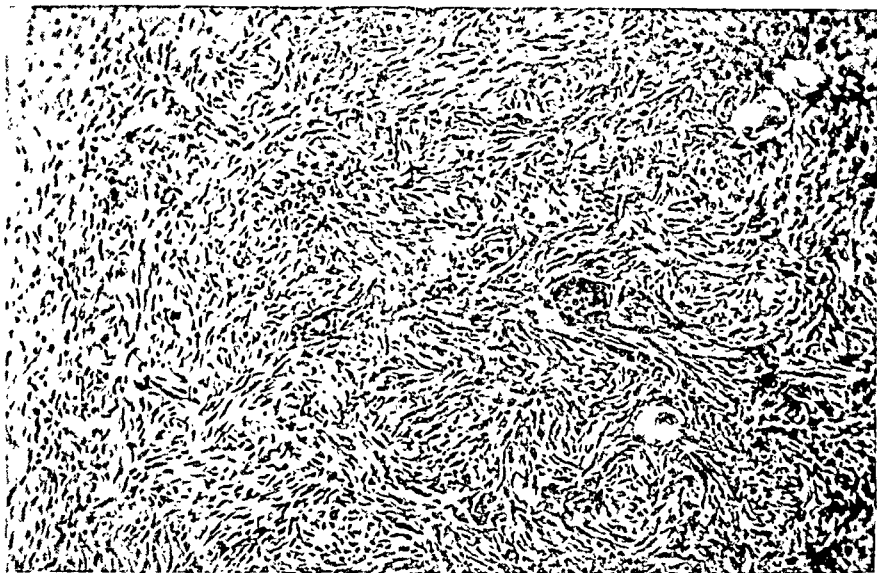


Fig. 9.—Photomicrograph of a portion of the cortex of the ovary seen in Fig. 8. Note the occasional apparently normal primordial follicles. $\times 130$.

were thin, with pale shrunken cells which showed no suggestion of activity. The medullary portion of the ovary was normal. In this patient the findings noted in the laboratory animals have been duplicated in the human being in a most satisfactory manner.

* * * * *

With this review of the laboratory and clinical investigations as a foundation let us attempt to evaluate androgenic therapy as to its advantages, disadvantages, indications, and contraindications.

ADVANTAGES AND DISADVANTAGES OF ANDROGENIC THERAPY IN GYNECOLOGY

The treatment of functional uterine bleeding with androgens has certain advantages. It is ambulatory which to many patients is a great convenience. It is perhaps the most effective of the nonsurgical measures available in the treatment of functional flow. There is no operative risk attached to its use. More important, so far as can be determined, there is a preservation of whatever reproductive ability the patient possesses. In event of subsequent pregnancies in a patient who

enlarged by the tumor, was pale. The Fallopian tubes appeared normal. There was no suggestion of pelvic engorgement or increased vascularity. The opened uterus showed a thin endometrium, not only in the region of the tumor but also far removed from it. Microscopic examination of the endometrium gave a more complete picture than had been possible



Fig. 7.—Photomicrograph of a section of the uterus showing the endometrium obtained from a patient who had had a hysterectomy because of fibromyomas. She had received 325 mg. of testosterone propionate during the fourteen days preceding operation. $\times 140$.



Fig. 8.—Section through the ovary of a patient who had received 325 mg. of testosterone propionate during the fourteen days preceding operation. The absence of recent follicles or young corpora lutea will be noted. $\times 5$.

treatment of disturbances of the climacteric as has been suggested by several authors.^{34, 46-48} However, the fact that androgens are at times effective appears on the basis of published reports to be indubitable. That this effect is the result of a depression of the pituitary gland seems most probable. Best results appear to be obtained when 30 to 50 mg. of testosterone propionate are injected weekly. Despite the fact that estrogenic substance is the logical agent to employ in the menopause there may be an occasional instance in which androgens would be preferable. As Kurzrok has pointed out this would be true of individuals who are allergic to estrogenic materials. It also may be advisable to turn to androgens rather than to large doses of estrogens for the treatment of either natural or surgical menopause in patients who are known to have had extensive endometriotic implants or other new growths. In these types of cases, a desire to relieve menopausal symptoms and yet to avoid the stimulating effect of estrogens may make a trial with male sex hormone worth while.

Information obtained from the literature^{49, 53, 58} suggests that androgenic therapy is indicated for the relief of primary (essential) dysmenorrhea where the discomfort is presumably due to painful uterine contractions in patients without demonstrable pelvic organic pathology to account for their distress. If further trial proves that testosterone will prevent menstrual molimen, its use in these often distressing cases will be strongly indicated.

Certain contraindications exist for the use of androgenic therapy in gynecologic practice. To attempt the management of uterine bleeding by any nonsurgical treatment, whether it be androgens, anterior pituitary-like preparations, or other therapy, without fully satisfying ourselves that organic abnormalities are absent, is hazardous. The presence of neoplasms, gross residues of infection, or retained products of gestation militate against the use of the male sex hormone. It is evident from the investigative work previously presented that definite masculinizing changes can occur when an excessive amount of testosterone propionate is administered. I feel very strongly that androgenic substances should not be given to a woman who presents notable android characteristics but that other means should be found for the management of her complaint. The presence of facial and pectoral hirsuties, especially on the upper lip and chin, or a heavy growth of coarse hair on the thighs, an unusually large clitoris or a deep voice are contraindications to androgenic therapy. Avoidance of the use of male sex hormone in such cases is advisable even though, almost without exception, the accentuation of masculinizing characteristics will disappear when the treatment is stopped.

The danger of overlooking organic pelvic disease in cases of uterine bleeding and dysmenorrhea, of serious breast pathology in mastalgias, and of systemic disorders associated with any of the conditions discussed should not go unmentioned. It need not be emphasized that there is always a considerable hazard of neglecting commonplace lesions when a new, effective, and at times startling therapeutic agent, such as androgenic therapy, is introduced.

has received testosterone, there is every reason to believe that normal offspring will be born and that these offspring will have normal reproductive powers. If androgenic therapy proves worthwhile in dysmenorrhea, afterpains, and menstrual molimen, the value of having a simple, innocuous, and effective treatment for these conditions requires no comment. The advantages resulting from the administration of male sex hormone in the routine treatment of menopausal disturbances seems somewhat questionable at this time.

Some disadvantages exist in the use of male sex hormone in women. First and most important is the very real danger of producing masculinizing phenomena when such materials are given in large doses to women who already possess android characteristics. The fact that these changes are temporary does not wholly overcome this disadvantage. A second disadvantage is that the treatment of functional uterine bleeding in many cases is not truly curative. In most instances, the flow is inhibited for many weeks, but there is a distinct tendency for the excessive bleeding to recur after a period of months has passed.

INDICATIONS AND CONTRAINDICATIONS TO THE USE OF ANDROGENIC THERAPY IN GYNECOLOGY

On the basis of the many reports in the literature^{33, 43-45, 76-78} and after having administered testosterone propionate to 22 women for the treatment of functional uterine bleeding, it is felt that there is a definite, although perhaps limited, place for androgenic therapy in the management of this disorder. It affords an almost certain means of inhibiting functional uterine flow. Its use appears indicated in women who do not have major pelvic pathology and in whom it is desirable to avoid extensive surgical procedures. This is particularly true of younger women in the childbearing years who are desirous of preserving their fecundity and of older women in whom the appearance of the climacteric within a relatively short time may be expected to put an end to excessive bleeding. There is no doubt that, of the many nonsurgical procedures now in use for functional menorrhagia, androgenic therapy may be expected to yield the most certain results. On a theoretical basis, inhibition of the menses by male sex hormone should be especially advantageous to women with pulmonary tuberculosis who suffer from an exacerbation of their chest pathology each time they menstruate.

If the work of Kurzrok and his associates is any criterion, androgenic therapy should be of value in premenstrual breast pain and in painful breasts during the early puerperium. While my experience in the use of testosterone propionate in the treatment of mastalgias and puerperal engorgement has been limited, it has been found efficacious in the few instances in which it was employed. It would appear that approximately one-half of the amount of testosterone used to inhibit uterine bleeding is effective in mastopathies and that 100 to 150 mg. will prevent post-partum breast engorgement in most cases.

In view of the logical and satisfactory management of the menopause with estrogens, it seems out of place to use male sex hormone in the

- (29) Nelson, W. O., and Gallagher, T. F.: *Science* 84: 230, 1936. (30) Demarest, E., and Capitain, Mme.: *Presse méd.* 45: 777, 1937. (31) Mazer, M., and Mazer, C.: *Endocrinology* 24: 175, 1939. (32) Freed, S. C., Greenhill, J. P., and Soskin, S.: *Proc. Soc. Exper. Biol. & Med.* 39: 440, 1938. (33) Foss, G. L.: *Lancet* 1: 992, 1938. (34) Binberg, C., Kurzrok, L., and Livingston, S.: *Endocrinology* 23: 243, 1938. (35) Zuckerman, S.: *Lancet* 2: 676, 1937. (36) Hartman, C. G.: *Proc. Soc. Exper. Biol. & Med.* 37: 87, 1937. (37) Zuckerman, S.: *Physiol.* 93: 15, *Proc.*, 1938. (38) Huffman, J. W., and Bos, L.: *Endocrinology* 26: 259, 1940. (39) Cotte, G., and Noel, R.: *Gynec. et obst.* 34: 294, 1936. (40) Kurzrok, R., and O'Connell, C. P.: *Endocrinology* 23: 476, 1938. (41) Greene, R. R., and Ivy, A. C.: *Science* 87: 200, 1937. (42) Mazer, C. M., and Mazer, M.: *Endocrinology* 24: 599, 1939. (43) Hamblen, E. C.: *J. Med. A. Georgia* 26: 368, 1937. (44) Geist, S. H., Salmon, U. J., and Gaines, J. A.: *Endocrinology* 23: 784, 1938. (45) Loeser, A. A.: *Lancet* 1: 373, 1938. (46) Kurzrok, L., Binberg, C. H., and Livingston, S.: *Endocrinology* 24: 347, 1939. (47) Mocquot, P., and Moricard, R.: *Bull. Soc. gynec. et d'obst.* 25: 787, 1936. (48) Margeil, E., and Zwilling, E.: *Polska gaz. lek.* 15: 815, 1936. (49) Rubenstein, H. S., and Abarbanel, A. R.: *AM. J. OBST. & GYNEC.* 37: 709, 1939. (50) Robson, J. M.: *Proc. Soc. Exper. Biol. & Med.* 36: 153, 1937. (51) McEuen, C. S., Selye, H., and Collip, J. B.: *Proc. Soc. Exper. Biol. & Med.* 36: 390, 1937. (52) *Idem*: *Ibid.* 36: 213, 1937. (53) Salmon, U. J., Geist, S. H., and Walter, R.: *AM. J. OBST. & GYNEC.* 38: 264, 1939. (54) Leonard, S. L., Sager, V., and Hamilton, J. B.: *Proc. Soc. Exper. Biol. & Med.* 37: 362, 1937. (55) McEuen, C. S., Selye, H., and Collip, J. B.: *Ibid.* 35: 56, 1936. (56) Selye, H., McEuen, C. S., and Collip, J. B.: *Ibid.* 34: 201, 1936. (57) Hamilton, J. B., and Wolfe, J. M.: *Ibid.* 36: 465, 1937. (58) Greenhill, J. P., and Freed, S. C.: *West. J. Surg.* 47: 301, 1939. (59) Robson, J. M.: *J. Physiol.* 92: 371, 1938. (60) Hertz, R., and Meyer, R. K.: *Endocrinology* 21: 756, 1937. (61) Papanicolaou, G. N., Ripley, H. S., and Shorr, E.: *Proc. Soc. Exper. Biol. & Med.* 37: 689, 1938. (62) Greene, R. R., Burrill, W. W., and Ivy, A. C.: *Ibid.* 38: 4, 1938. (63) Gray, L. A., and Lawson, H.: *Ibid.* 41: 108, 1939. (64) Folley, S. J., and Kon, S. K.: *Proc. Roy. Soc., B.* 124: 476, 1938. (65) Gaines, J. A., Salmon, U. J., and Geist, S. H.: *Proc. Soc. Exper. Biol. & Med.* 38: 779, 1938. (66) Nathanson, I. T., Franseen, C. C., and Sweeney, A. R.: *Ibid.* 39: 385, 1938. (67) Magistris, H.: *Compt. rend. soc. de Biol.* 117: 455, 1934. (68) Guerico, F.: *Atti Soc. ital. ostet. e ginec.* 35: 353, 1939. (69) Spence, A. W.: *Lancet* 2: 817, 1939. (70) Abarbanel, A. R.: *AM. J. OBST. & GYNEC.* 38: 1043, 1939. (71) Shay, H., Gershon, C. J., Paschis, K. E., and Fils, S. S.: *Endocrinology* 25: 933, 1939. (72) Siegler, S. L., and Silverstein, L. M.: *AM. J. OBST. & GYNEC.* 39: 109, 1940. (73) Binberg, C. H., Kurzrok, L., and Klor, S. J.: *Ibid.* 39: 107, 1940. (74) Burrows, H.: *J. Path. & Bact.* 45: 311, 1937. (75) Klein, M., and Parkes, A. S.: *Proc. Roy. Soc. London* 121: 574, 1937. (76) Cotte, G., Martin, J. F., and Mankiewicz, E.: *Gynécologie* 36: 561, 1937. (77) Rubenstein, H. S.: *J. A. M. A.* 112: 537, 1939. (78) Sturgis, W. C., Abarbanel, A. R., and Nades, N. S.: *AM. J. OBST. & GYNEC.* 39: 102, 1940. (79) Astwood, E. B., Geschichter, C. F., and Rousch, E. O.: *Am. J. Anat.* 61: 373, 1937. (80) Portes, L., Dalsace, J., and Wallich, R.: *Compt. rend. Soc. de Biol.* 130: 1100, 1939. (81) Lacassagne, A., and Raynaud, A.: *Ibid.* 130: 689, 1939. (82) Salmon, U. J.: *Endocrinology* 23: 779, 1938. (83) Courrier, R., and Gros, G.: *Compt. rend. Soc. de Biol.* 127: 921, 1938. (84) Nelson, W. O., and Merchel, C. G.: *Ibid.* 36: 823, 1937. (85) Wolff, E., and Ginglinger, A.: *Compt. rend. Soc. de Biol.* 121: 1476, 1936. (86) Korenchevsky, V., Dennison, M., and Simpson, S.: *Biochem. J.* 29: 2534, 1935. (87) Klein, M.: *Compt. rend. Soc. de Biol.* 127: 915, 1938. (88) Korenchevsky, V., Hall, K., and Burbank, R.: *Biochem. J.* 33: 372, 1939. (89) Loeser, A. A.: *Brit. M. J.* 1: 479, 1940. (90) Greenblatt, R. B.: *J. A. M. A.* 115: 120, 1940. (91) Abarbanel, A. R.: *Endocrinology* 26: 765, 1940. (92) Greenhill, J. P., and Freed, S. C.: *AM. J. OBST. & GYNEC.* 39: 636, 1940.

DISCUSSION

DR. CARL R. MOORE.—About twenty years ago we believed strongly in the specificity of sex hormones, in particular in the reactions of specific sex structures to homologous hormones. But as potent tissue extracts and pure chemical hormones became available, we learned from experiment that opposite sex hormones did exert some type of effect. We can, therefore, consider the biologic reactions and therapeutic properties of male sex hormones for gynecologic disorders.

SUMMARY

Effects in 22 women who received androgenic therapy parallel those produced in laboratory animals by injections of testosterone propionate. In my cases, functional uterine bleeding was inhibited by the male sex hormone. In this group, no notable masculinizing changes developed, except occasional temporary hypertrophy of the clitoris. Three of these patients have been under observation for more than two years.

Testosterone propionate will bring about a cessation of genital activity in human beings as it has been observed to do in the adult female rabbits and rats. This effect is the result of pituitary rather than ovarian inactivation. The changes produced by the male sex hormone are temporary, with resumption of cyclic phenomena in the genitalia after administration is discontinued. When large doses of testosterone propionate (over 350 to 500 mg.) are injected over a considerable period of time, temporary masculinizing changes, especially hypertrophy of the clitoris, may appear. Inhibition of activity in the lactating breast after the administration of testosterone propionate has been observed clinically and has been demonstrated histologically in animals. Reports in the literature indicate that reproduction is possible and that normal young have been born to human beings who have received male sex hormone prior to their pregnancies.

There is considerable evidence to suggest that androgenic therapy has a place in the treatment of functional uterine bleeding, mastalgias and puerperal breast engorgement, and for the inhibition of lactation. Further investigation of its use in dysmenorrhea and the treatment of menstrual molimina seems indicated. The use of male sex hormone may, perhaps, be advantageously used in preference to the estrogens in certain selected instances of menopausal disturbances.

REFERENCES

- (1) *Varangot, J.*: Ann. d'endocrinol. 1: 55, 1939. (2) *Ihrke, I. A., and D'Amour, F. E.*: Am. J. Physiol. 96: 289, 1931. (3) *Moore, C. R., and Price, D.*: Am. J. Anat. 50: 13, 1932. (4) *Hamilton, J. B., and Wolfe, J. M.*: Endocrinology 22: 360, 1938. (5) *Wolfe, J. M., and Hamilton, J. B.*: Ibid. 21: 603, 1937. (6) *Friedgood, H. B., and Dawson, A. B.*: Ibid. 22: 674, 1938. (7) *Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 37: 488, 1937. (8) *Browman, L. G.*: Ibid. 36: 205, 1937. (9) *Robson, J. M.*: Ibid. 35: 49, 1936. (10) *Papanicolaou, G. N., and Shorr, E.*: AM. J. OBST. & GYNEC. 31: 806, 1936. (11) *Shorr, E., Papanicolaou, G., and Stimmel, B.*: Proc. Soc. Exper. Biol. & Med. 38: 759, 1938. (12) *Papanicolaou, G. N., Ripley, H. S., and Shorr, E.*: Endocrinology 24: 339, 1939. (13) *Robson, J. M.*: Proc. Soc. Exper. Biol. & Med. 35: 49, 1936. (14) *Korenchevsky, V., and Hall, K.*: J. Path. & Bact. 45: 681, 1937. (15) *Korenchevsky, V., Dennison, M., and Hall, K.*: Biochem. J. 31: 780, 1937. (16) *McKeown, T., and Zuckerman, S.*: Proc. Roy. Soc. London, S.B. 124: 362, 1937. (17) *Deanesley, R., and Parkes, A. S.*: Brit. M. J. 1: 257, 1936. (18) *Phelps, D., Burch, J. C., and Ellison, E. T.*: Endocrinology 23: 458, 1938. (19) *Wolfe, J. M., and Hamilton, J. B.*: Proc. Soc. Exper. Biol. & Med. 37: 189, 1937. (20) *Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 38: 352, 1938. (21) *Williams, C., Phelps, D., and Burch, J. C.*: Endocrinology 25: 312, 1939. (22) *Engle, E. T., and Smith, P. E.*: Ibid. 25: 1, 1939. (23) *Nathanson, I. T., and Towne, L. E.*: Ibid. 25: 754, 1939. (24) *Greenhill, J. P., and Freed, S. C.*: J. A. M. A. 112: 1573, 1939. (25) *Nelson, W. O., and Gallagher, T. F.*: Anat. Rec. 64: 129, 1930. (26) *Scipades, E.*: Proc. Soc. Exper. Biol. & Med. 37: 24, 1937. (27) *Demarest, E., and Capitain, Mme.*: Presse méd. 46: 185, 1938. (28) *Reese, R. P., and Mizner, J. P.*: Proc. Soc. Exper. Biol. & Med. 40: 66, 1939.

pain which occurs in the breasts before the menses, to relieve some cases of dysmenorrhea and to prevent premenstrual tension in some cases. To control or suppress uterine bleeding, it is necessary to give between 300 and 500 mg. throughout an entire period, whereas for dysmenorrhea, premenstrual painful breasts, and premenstrual tension only about 150 mg. divided in six doses during the last two weeks of the menstrual cycle usually suffice. In most of the cases, the beneficial results are only temporary. In a few cases, however, the good results persist for a few months after two or three series of injections are given. Recently Dr. Freed and I have been using ammonium chloride to overcome premenstrual distress, and we have obtained most encouraging results with this simple, and inexpensive form of therapy.

I should like to emphasize the caution urged by Drs. Huffman and Moore. Large doses of testosterone propionate sometimes produce virilism effects, such as increased hair growth on the face, lowering of the pitch of the voice, and slight enlargement of the clitoris. In addition, many women gain weight and develop an acneform eruption. Fortunately all of these disagreeable effects disappear after the hormone is stopped.

DR. HUFFMAN (closing).—In a few instances, too few to report, we have noted satisfactory results in premenstrual breast pain after giving 25 mg. of testosterone propionate intramuscularly twice weekly for two weeks preceding menstruation. This has a temporary effect during the following menstrual period and must be repeated each month.

We have not been as fortunate as Dr. Greenhill in obtaining a permanent cure of functional uterine bleeding by means of injections of testosterone propionate. As months go on after a series of injections the patients tend to get a recurrence of prolonged flow. However, with the dosages we have been using (300 to 400 mg.) we have seen no masculinizing characteristics develop other than occasional hypertrophy of the clitoris. This hypertrophy disappeared entirely within two or three weeks after cessation of the therapy.

On logical grounds one may be somewhat puzzled to account for male hormone action in females. Thus, following male hormone administration, we may have suppression of estrus cycles, suppression of lactation, prolongation of gestation, or prevention of delivery and the prevention of menstrual bleeding. On the clinical side, we have reports that male hormone alleviates menopausal symptoms, aids in dysfunctional, as well as functional bleeding, and is efficacious in prevention of lactation.

In attempting to organize our conceptions, it appears that the mechanism of these results may fall into at least two main categories. The first of these has to do with action of the male hormone on the pituitary gland, while the second involves local or direct action on the end organs concerned. It is not always clear which of these may be involved, and indeed it is possible both are frequently involved.

It should be recalled first that the stimulus inciting activity in the sex glands is the pituitary body. At the same time the sex hormones produced exert an influence back upon the pituitary. This latter influence may be inhibitory in the direct sense and in some cases may be considered to introduce qualitatively different secretions on the part of the pituitary.

Suppose we look for a moment at the estrus cycle. If ovaries are removed, cycles are abolished; pituitary removal produces similar results; male hormone likewise suppresses them. In each case the lack of estrogenic substances is largely responsible. Cycles could also be abolished by injecting estrogens so far as pituitary suppression is concerned, but now by direct action the estrogens affect the uterus and vagina and bring them into a constant estrous condition. Male hormones likewise suppress the pituitary but do not stimulate the estrus response of the uterus. These aspects are of interest in the clinical treatment of menopausal symptoms. Presumably the direct causal agent of these symptoms is lack of the estrogenic substances to inhibit the pituitary. The excessive pituitary secretion should be suppressed by either male or female hormones. When estrogenic therapy is employed, it is to be expected that these substances will activate the uterus, and perhaps maintain an hypertrophied state. Male hormone will suppress the pituitary and not stimulate the uterus, and hence would appear ideal in some respects.

In a similar manner lactation is abolished by male hormone, apparently because of pituitary depression. Male hormone also decreases uterine motility; but whether this is due entirely to pituitary suppression, giving an indirect estrogenic suppression or is due to a direct action on uterine musculature is not certainly known. Certain phenomena of dysmenorrhea may be influenced by male hormone. It is not clear why it would be preferable to an estrogen in controlling pituitary activity for this condition, unless it be the fact that the addition of estrogens might further enhance a hypersensitive uterus.

Danger of injury to offspring conceived much later than androgenic treatment is unlikely, for hormone storage in the body does not occur and hormones as effective agents in modification of developing young act directly. On the other hand, although we do not know conditions in the human development, it is possible, as indicated by other experimentation, that serious developmental injuries to the reproductive system might follow treatments with male hormone during pregnancy.

In any treatment with sex hormones, androgens or estrogens, therefore, the action upon the pituitary, which typically reduces or abolishes ovarian secretions, as a secondary effect, constitutes one avenue of effectiveness, while the possible direct action on end organs or on general conditions constitutes another. This latter may not only involve reactions or responses on the part of the end organ in question but one must always consider such side effects as general heightening of masculine tendencies. These, especially if severe, may decidedly offset any advantageous responses on the part of the condition being treated.

DR. J. P. GREENHILL.—Clinically the male hormone has been found helpful to control or suppress abnormal uterine bleeding, to diminish the swelling and

groups although, of course, there is some overlapping. The largest group (Tables I and IA) consists of 26 patients with a chief complaint of sterility. The second group (Table II) of 6 patients complained of dysfunctional flowing, and the third group (Table III) of 16 patients complained of amenorrhea.

In 36 of the 48 cases, the diagnosis of ovulation or anovulation was made before treatment by endometrial biopsy, taken a few days prior to the onset of menstruation, and often repeated several times. Attempts at biopsy in 3 of the remaining 12 cases yielded insufficient material on one or more attempts. Nine patients, for various reasons, were not biopsied.

Since the effective dosage of equine gonadotropic hormone in the human being is not definitely known (Hart and Cole⁵² found that ovarian weight rather than the body weight is the criterion for determining comparative doses in animals), treatment was given with greatly varying doses in several different ways:

1. A single injection of this hormone was given on the seventh to the twelfth day of the menstrual cycle. An injection contained 200 to 600 rat units.
2. A course, consisting of 4 to 10 injections, was given daily or on alternate days, usually in the early part of the cycle, just previous to the time when ovulation was expected to occur.
3. Courses were given in the same way, but chorionic gonadotropic hormone (C.G.H.) was given in 500 rat unit doses with each injection of equine gonadotropic hormone.
4. Courses of equine gonadotropic hormone followed immediately by courses of equine gonadotropic hormone and chorionic gonadotropic hormone were tried.
5. Combinations of courses of equine gonadotropic hormone preceded by, concurrently with, or followed by synthetic estrogen or estrogenic hormone were given.

The intravenous route of administration was employed in 18 patients and the intramuscular method in the others. Chorionic gonadotropic hormone was given intramuscularly. Before each course of injections, patients were skin-tested for sensitivity to horse serum. We feel that this is wise despite the fact that equine gonadotropic hormone preparations have been highly purified and the protein content greatly reduced, and despite Hawkinson's⁴⁹ statement that skin testing "seems to be obviated after demonstrating that rabbits, previously sensitized with injections of gonadin, showed no evidence of serum protein reaction after injection of one cubic centimeter of gonadin intravenously." Three of our patients (U 142, U 681 and U 1346) showed such strongly positive skin tests, after receiving from one to five courses of equine gonadotropic hormone, that further similar therapy was omitted. Another patient (U 1790) had urticaria at the site of injection following therapy. Four other patients complained of nausea and vomiting, abdominal pain, headache or backache which they attributed to the injections.

Careful study of the fact that three patients showed the presence of cysts of the ovary after treatment with equine gonadotropic hormone, has failed to convince us that there was any causal connection between the treatment and the diseased condition. However, Sevringhaus^{21, 51, 46} warns that continuous therapy with equine gonadotropic hormone can cause cystic follicles in the monkey ovaries, and may do so in the human ovaries. Watson⁴¹ feels convinced that equine gonadotropic hormone therapy resulted in cysts of the ovaries in his cases. Therefore, this possibility must be kept in mind.

CLINICAL EXPERIENCES WITH EQUINE GONADOTROPIC HORMONE

HENRY W. ERVING, M.D., CHRISTINE SEARS, M.D., AND
JOHN ROCK, M.D., BROOKLINE, MASS.

(From the Sterility and Endocrine Clinic, Free Hospital for Women)

INTRODUCTION

SINCE 1937 there have appeared 14 clinical reports on the use of equine gonadotropic hormone (E.G.H.). Hamblen,^{27, 45} on two occasions, Frank,⁴⁰ and Watson, Smith and Kurzrok⁴¹ are the only ones to report consistently negative results following administration of the hormone. The other 10 reports are by Bowes,³⁹ Davis and Koff,⁴² Siegler and Fein,²³ Campbell and Sevringhaus,^{46, 51} Kennedy and Shelton,⁴⁷ Hall,⁴⁸ Hawkinson,⁴⁹ Rubenstein,⁵⁰ and Gray.⁷ Although they admit failures, they have all expressed either enthusiasm or optimism about this new gonadotropic hormone. We feel that none of these reports offers conclusive evidence of the value of equine gonadotropic hormone in stimulating ovulation in women, and that our own results bear out this contention.

CLINICAL STUDY

In our study we used equine gonadotropic hormone, gonadin, prepared by the Cutter Laboratories, and in two cases supplemented this with anteron, prepared by the Schering Corporation.

Gonadin is dispensed in solution and each cubic centimeter contains 200 rat units. According to the Cutter Laboratories, a rat unit is "the amount of hormone which, when injected subcutaneously in a single dose into five immature female rats (twenty-one to twenty-three days of age), will produce an average of from 3 to 10 large follicles or corpora lutea at the time of autopsy ninety-six hours later, and half of which will not produce this average in another group of 5 rats similarly treated."

Anteron is dispensed in the form of dry stable pellets and its potency is expressed in international units. The Permanent Commission on Biological Standardization of the Health Organization of the League of Nations states that "the specific gonadotropic activity of 0.25 mg. (250 gammas) of the standard preparation shall be the international unit for recording the activities of all gonadotropic preparations of the serum of pregnant mares, but only of such."

New batches of gonadin were received frequently during this study to avoid the possibility of diminished potency, and the anteron was received a few days prior to its use.

The 48 cases in this study comprise 21 private and 27 clinic patients seen over periods ranging from six months to eight years. They fall roughly into three

TABLE I—CONT'D

PA- TIENT	AGE	YEARS MAR- RIED	CHIEF COM- PLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	MENSTRUAL HABIT	STERILITY WORKUP	THY- ROID	EQUINE GONADOTROPIC HORMONE	RESULTS
U681	30	10	Sterility 6 yr. 1930 Misc. 7 mo. 1933 Abo. 3 mo.	Negative 1931 Appendectomy 1933 Suspension 1939 D. & C. B.M.R. -7	Irregular periods every 26-39 days, often pro- longed	Biopsy: Proliferative endometrium Rubin: - Huhner: 1 test unsatisfactory Husband: Normal	1 gr. daily	1200 R.U. 5 doses 14th-18th days 1200 R.U. 5 doses 8th-12th days	No change Biopsy: Prolif. endome- trium No change
U1870	28	9	Sterility 6 yr. Normal delivery, full term, 1933	Negative	Normal period every 25-26 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	-	1200 R.U. 5 doses 8th-12th days	No change
2139	36	1	Sterility 1 yr. 1939 abortion 6 wk. ?	Negative	Normal period every 25-28 days	Biopsy: - Rubin: Tubes patent Huhner: Motile sperm found Husband: -	1½ gr. daily	*200 R.U. 9th day	Pregnant Normal delivery
2013	27	3	Sterility 1 yr. Dia- phragm 2 yr.	Negative 1939 D. & C. B.M.R. -3 to +2	Normal period every 29-34 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: -	1 gr. daily	*100 R.U. 7th day 400 R.U. 7th day 1800 R.U. 4 doses 8th-10th-12th-13th days	No change No change No change
890	26	5	Sterility 2½ yr. Condom 1 yr. Rhythm and douches 1½ yr.	Negative 1938 Conization cervix B.M.R. +4	Normal period every 26-28 days	Biopsy: None Rubin: Tubes patent Huhner: Motile sperm found Husband: Oligospermia	-	*200 R.U. 10th day	No change

TABLE I. STERILITY TREATED WITH EQUINE GONADOTROPIC HORMONE ALONE

PATIENT	AGE	YEARS MAR- RIED	CHIEF COM- PLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	MENSTRUAL HABIT	STERILITY WORKUP	THY- ROID	EQUINE GONADOTROPIC HORMONE	RESULTS
U1852	28	2	Sterility 2 yr.	Negative B.M.R. -6	Normal period every 28-32 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	-	*1200 R.U. 5 doses 8th-12th days 1200 R.U. 5 doses 8th-12th days	No change No change
U1794	25	5	Sterility 5 yr.	Obese B.M.R. -1	Normal period every 28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	800 R.U. 2 doses 8th-9th days 2400 R.U. 5 doses 8th-12th days	No change No change
U1781	27	6	Sterility 6 yr.	Obese 1922 Appendectomy with drainage B.M.R. +23	Normal period every 28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	-	1200 R.U. 5 doses 8th-12th days 1200 R.U. 5 doses 8th-12th days	No change No change
2182	30	1½	Sterility 1½ yr.	Negative 1933 Appendectomy 1939 D. & C., resec- tion ovaries, sus- pension	Normal period every 28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: -	-	1200 R.U. 5 doses 8th-12th days	No change
1005	23	5	Sterility 1½ yr. 1938 abortion 4 mo.	Negative 1936 D. & C. 1938 Vag. Hys. for missed abortion 1939 resection ovaries, suspen- sion, appendec- tomy	Normal period every 26-28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	200 R.U. 12th day 1200 R.U. 5 doses 8th-12th days 1200 R.U. 3 doses 7th-9th-11th days 2000 R.U. 4 doses 7th-10th days	No change No change Period 8 days late No change

* Intravenous.

TABLE IA. STERILITY TREATED WITH EQUINE GONADOTROPIC HORMONE AND ESTROGEN

PA-TIENT	AGE	YEARS MAR-RIED	CHIEF COM-PLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	MENSTRUAL HABIT	STERILITY WORKUP	THY-ROID	E.G.H. AND ESTROGENIC SUBSTANCE	RESULTS
2248	33	9	Sterility 9 yr.	Negative	Normal period every 25-28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Unsatisfactory Husband: Count normal, treated for chronic prostatitis	1 gr. daily	Stilbestrol 1 mg. daily for 2 cycles. With 1st cycle E.G.H. 1200 R.U. 5 doses 10th-14th days	No change
2370	33	2	Sterility 2 yr.	Negative	Normal period every 28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	Stilbestrol 1 mg. daily for 2 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 1200 R.U. 5 doses 7th-11th days	No change No change Flowed 14 days later Biopsy: 33 days later: Sec. End.
2174	37	6	Sterility 6 yr.	Negative	Normal period every 27-30 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	2 gr.	Stilbestrol 1 mg. daily x 30. Then E.G.H. 1200 R.U. 5 doses 8th-12th days	Period on schedule but pro-fuse and painful
996	33	4	Sterility 1½ yr. 1938 abortion 3 mo.	Negative 1938 D. & C.	Normal period every 26 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	Stilbestrol 1 mg. daily for 3 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 1000 R.U. 5 doses 7th-11th days	No change No change

* Intravenous.

E. G. H., Equine gonadotropic hormone.

E., Estrogenic hormone.

705	34	7	Sterility 7 yr.	Negative 1938 D. & C., resec- tion both ovaries, suspension, ap- pendectomy.	Periods irregu- lar for 5 years; every 30-40 days last year	Biopsy: Proliferative endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: -	1½ gr. daily	*100 R.U. 15th day *300 R.U. 9th day	No change No change Biopsy: 4 mo. later, secretory endome- trium
2369	39	11	Sterility 3 yr. 1928 abortion 6 wk. 1930, normal delivery 1931, abortion 3 mo. 1933, normal delivery Dia- phragm 3 yr.	Negative	Normal period every 28-32 days	Biopsy: - Rubin: Tubes patent Huhner: Motile sperm found Husband: -	1 gr. daily	1800 R.U. 4 doses 9th-12th days	No change
1022	30	6	Sterility 6 yr.	Negative 1930 Appendectomy 1937 Hymenectomy	Normal period every 26-29 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	-	*100 R.U. 10th day	No change
2156	24	7	Sterility 3 yr. Condom 4 yr.	Negative	Normal period every 28-29 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	-	400 R.U. 11th day	Flowed 8 days later Biopsy: 27 days later: Secretory endome- trium

TABLE 1A—CONT'D

PATIENT	AGE	YEARS MAR- RIED	CHIEF COM- PLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	MENSTRUAL HABIT	STERILITY WORKUP	THY- ROID	E.G.H. AND ESTROGENIC SUBSTANCE	RESULTS
2265	25	5	Sterility 3 yr. 1936 misc. 6½ mo.	Negative 1931 appendectomy 1938 D. & C.	Normal period every 28 days	Biopsy: Proliferative endometrium Rubin: Tubes patent Huhner: Unsatisfactory Husband: Normal	1 gr. daily	E. 600 I.U. daily for 2 cycles. With 2nd cycle E.G.H. 1200 R.U. 5 doses 7th- 11th days E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 1800 R.U. 4 doses 7th-10th days	No change No change No change
2099	37	9	Sterility 9 yr.	Negative	Normal period every 33-35 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: -	-	E. 600 I.U. daily for 3 cycles. Then *E.G.H. 800 R.U. 3 doses 9th-11th- 13th days	No change
2264	34	?	Sterility 3 yr. 1936, normal delivery full term	Negative	Normal period every 28-30 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: -	1 gr. daily	E. 2000 I.U. daily for 3 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 1800 R.U. 4 doses 7th-10th days	No change No change No change
2115	38	13	Sterility 13 yr. 1½ yr. since opera- tion	Negative 1938 salpingostomy, resection l. ovary, suspension	Irregular pe- riod every 25-52 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	E. 600 I.U. daily × 28. Then E.G.H. 1200 R.U. 5 doses 8th-12th days	No change

U1771	34	12	Sterility 11 yr. 1927 abortion 3 mo.	Negative	Normal period every 28-30 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	Stilbestrol 1 mg. daily × 30 and E.G.H. 1200 R.U. 5 doses 7th-11th days E.G.H. 400 R.U. 1 dose 7th day	No change
U2871	26	3	Sterility 3 yr.	Negative B.M.R. -19	Normal period every 28-30 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	1 gr. daily	E.G.H. 1600 R.U. 3 doses 11th-12th- 14th days Stilbestrol .1 mg. daily for 2 cycles. With 2nd cycle E.G.H. 2400 R.U. 4 doses 7th-10th days	Period on schedule but pro- fuse and prolonged No change
U655	23	5	Sterility 5 yr.	Negative B.M.R. -13	Irregular for 5 years 28-60 days. Period every 28-30 days while attend- ing clinic	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	3 gr. daily	Stilbestrol .1 mg. daily × 55. With 2nd cycle E.G.H. 1200 R.U. 5 doses 8th-12th days	No change
2334	34	2½	Sterility 1 yr. 1938 abortion 3 mo.	Negative	Normal period every 25-28 days	Biopsy: Secretory endometrium Rubin: Tubes patent Huhner: Motile sperm found Husband: Normal	½ gr. daily	Stilbestrol 1 mg. daily × 20 and E.G.H. 1200 R.U. 5 doses 8th-12th days E.G.H. 1200 R.U. 5 doses 8th-12th days	No change

TABLE II. DYSFUNCTIONAL BLEEDING TREATED WITH EQUINE AND CHORIONIC GONADOTROPIC HORMONES

PATIENT	AGE	MARITAL STATUS	CHIEF COMPLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	MENSTRUAL HABIT	BIOPSY PREVIOUS THERAPY	TIROID	HORMONE THERAPY	RESULTS
U2875	14	S	Dysfunctional flow-ing	Negative B.M.R. -17	Frequent prolonged periods of flow for 2 years. Persistent flowing for 3 months	No biopsy C.G.H. and testosterone propionate ineffective	2 gr. daily	*E.G.H. 600 R.U. and C.G.H. 1500 R.U. in 3 doses while flowing	Flow stopped day after last injection for 8 days. Then 10 days flowing, 6 days no flow, 5 days flow Amenorrhea 3 months No biopsy No evidence of ovulation
U2876	23	S	Dysfunctional flow-ing	Negative 1933 D. & C., Rt. oophorectomy, appendectomy B.M.R. -4	Prolonged periods for 6 years. Past year only 3-10 days between periods	Biopsy: Proliferative endometrium with dysplasia. C.G.H., "Maturity Factor," theelin ineffective		*E.G.H. 800 R.U. in 4 doses alt. days while flowing; 1 week later *E.G.H. 800 R.U. & C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 600 R.U. & C.G.H. 1500 R.U. in 3 doses alt. days while flowing	Flow more profuse Flow stopped for 3 weeks Flow stopped for 5 days No evidence of ovulation

*Intravenous.

E. G. H., Equine gonadotropic hormone.

C. G. H., Chorionic gonadotropic hormone.

Each of our patients was examined in the gynecologic clinic before presenting herself at the endocrine clinic, and all abnormalities such as retroversion, infected cervixes, vaginitis, etc., were taken care of. Thyroid was given to most of the patients, even without determination of the basal metabolic rate, unless there were definite contraindications.

GROUP I. STERILITY (TABLES I AND IA)

In this group of 26 patients, the ages varied from 23 to 39, and the duration of sterility from one to eleven years. Ten patients were known to have been pregnant one or more times before, and 3 of these had had full-term deliveries. Eight had had abdominal operations. All but 3 had "normal" regular periods. There were 3 cases with anovulatory cycles, and 20 with ovulatory cycles as shown by biopsy. Of the remaining 3 cases, 1 patient became pregnant before biopsy could be done, and the other 2 were not biopsied. Patency of the tubes was proved by insufflation in all cases except one in which no Rubin test was made. Motile sperm were found in the cervix four to twenty hours following coitus in all but 3 patients, and the husbands in these cases were examined and found to be normal. Husbands were given complete physical examinations in most instances, and semen specimens alone were examined in others.

The group is divided into two parts on the basis of therapy. The purpose of giving the equine gonadotropic hormone was to repeat the work of Hall⁴⁸ and of Davis and Koff,⁴² i.e., to stimulate the ovaries and cause multiple ovulation if possible, in the hope of increasing the chances of pregnancy. The addition of estrogenic hormone or synthetic estrogen in the cases in Table IA was intended to prime the genital system or act as a tonic to it, and thus to aid impregnation. It was also given in order to duplicate conditions of clinical experiments done elsewhere.

Results were very disappointing. One patient (Case 2139) became pregnant immediately following a course of equine gonadotropic hormone. However, as this patient only two months before had had an unusually heavy flow two weeks after her period was due, which had been diagnosed as a possible abortion, we do not feel that her pregnancy was related to the therapy. One of the patients with anovulatory bleeding (705) had a secretory endometrium four months after treatment, but as the total amount of equine gonadotropic hormone received was only 400 R.U., given in two monthly injections, it seems more reasonable to us to assume that she had occasional anovulatory cycles which, as Rock, Bartlett and Matson⁵⁴ and Novak²² point out, are not unusual.

In 2 patients (Cases 1022 and 2013), cysts of the ovaries were noted following treatment. Both followed the intravenous injection of only 100 R.U. of equine gonadotropic hormone. In Case 1022, painful and enlarged ovaries were not found until seven months after treatment. At laparotomy, three months later, ten months after treatment, follicular cysts were excised from both ovaries, and the patient became pregnant one month later, which is not uncommon under these conditions.²⁸ In Case 2013, a cyst was not noted until four months after treatment. It was purposely ruptured while the patient was having a dilatation and curettage. Six months later, and two months after 400 R.U. more of equine gonadotropic hormone had been given, the ovary again was noted to be cystic.

There was no noteworthy change in the remaining twenty-two patients after equine gonadotropic hormone administration.

GROUP II. DYSFUNCTIONAL FLOWING (TABLE II)

This group consists of 6 patients ranging in age from 14 to 28. Three were single and 3 married, with no known pregnancies. Four had had one or more curettages. Dysfunctional flowing had persisted from eighteen months to eight years. Biopsies were omitted on 2 patients aged 14 and 16 with unruptured hymens. Of the remaining 4 patients, 2, prior to treatment, showed proliferative endometrium with dysplasia, one had hyperplasia, and the last had a normal

TABLE III. AMENORRHEA TREATED WITH EQUINE AND CHORIONIC GONADOTROPIC HORMONES

PATIENT	AGE	MARITAL STATUS	CHIEF COMPLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	BIOPSY MENSTRUAL HABIT	THYROID	HORMONE THERAPY	RESULTS	BIOPSY
U1353	18	S	Amenorrhea (primary)	Hypoplasia of genital organs 1938 D. & C. B.M.R. -80 to -17	Never menstruated Biopsy: no material obtainable at D. & C.	3 gr. daily	*E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days Stilbestrol 1 mg. daily x 7 mo. Stilbestrol 2 mg. daily x 60. Then *E.G.H. 800 R.U. in 3 doses alt. days *E.G.H. 1000 R.U. in 4 doses alt. days *E.G.H. 1200 R.U. in 4 doses alt. days *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 1200 R.U. in 6 doses alt. days followed by *E.G.H. 1200 R.U. and C.G.H. 3000 R.U. in 6 doses alt. days E.G.H. 1200 R.U. in 5 daily doses	No flow Flowed 1 time during administration and after withdrawal No flow No evidence of ovulation No flow No flow No evidence of ovulation No flow No evidence of ovulation	No flow Prolif. End.
U1792	25	S	Amenorrhea (primary)	Hypoplasia of genital organs B.M.R. +17 to +1	Never menstruated Biopsy: no material obtainable in 2 attempts	2 gr. daily	*E.G.H. 1000 R.U. in 4 doses alt. days *E.G.H. 1200 R.U. in 4 doses alt. days *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 1200 R.U. in 6 doses alt. days followed by *E.G.H. 1200 R.U. and C.G.H. 3000 R.U. in 6 doses alt. days E.G.H. 1200 R.U. in 5 daily doses	No flow No flow No flow No flow No evidence of ovulation	Insufficient tissue Hypoplasia Hypoplasia
U1790	22	S	Amenorrhea (primary)	Hypoplasia of genital organs B.M.R. -16	Never menstruated No biopsy	--	E.G.H. 1200 R.U. in 5 daily doses	No flow No evidence of ovulation	
U1791	22	S	Amenorrhea	Hypoplasia of genital organs Masculine distribution of hair B.M.R. -16	Few scanty periods since onset at 15 Biopsy: Proliferative endometrium	3 gr. daily	Stilbestrol 1 mg. daily x 21 Then E.G.H. 1200 R.U. in 5 doses 7th-11th days	Withdrawal bleeding No flow No evidence of ovulation	Prolif. End.
U1783	23	S	Amenorrhea	Hypoplasia of genital organs B.M.R. -28	No periods for 2 years Biopsy: Hypoplasia	3 gr. daily	*E.G.H. 1000 R.U. in 4 doses alt. days	No flow No evidence of ovulation	2 wk. later hypoplasia 3 wk. later hypoplasia

*Intravenous.

E.G.H., Equine gonadotropic hormone.

C.G.H., Chorionic gonadotropic hormone.

U1797	27	Mar- ried 6 yr.	Dys- func- tional flow- ing	Negative 1936 D. & C. B.M.R. -11	For 8 years irregular periods lasting from 10 days to a month	Biopsy: Proliferative endometrium with dysplasia. X-ray, C.G.H., testosterone propionate ineffec- tive	*E.G.H. 1000 R.U. in 4 doses alt. days 23rd-30th days	Flowed after first in- jection and continued for 18 days No evidence of ovula- tion
U1863	28	Mar- ried 5 yr.	Dys- func- tional flow- ing	Obese 1938 D. & C. B.M.R. -8	For 22 months pro- longed periods and intermenstrual staining. Relieved by D. & C. for 1 month	Biopsy: Proliferative endometrium with hyperplasia	E.G.H. 1200 R.U. in 5 doses daily 23rd-27th days	Profuse and prolonged flow 3 days, begin- ning 3 days later Biopsy: Proliferative endometrium No evidence of ovula- tion
2143	20	Mar- ried 1 yr.	Dys- func- tional flow- ing	Negative 19 7 D. & C. 1934 D. & C. Appendectomy	Always very irregular. For 3 years pro- longed periods	Biopsy: Proliferative endometrium	E.G.H. 1000 R.U. in 5 doses 6th-10th days followed by Stilbes- trol 1 mg. daily x 9	No change in menstrual habit No evidence of ovula- tion
U142	16	S	Dys- func- tional flow- ing	Uterus small B.M.R. +7 Hg 54%	Periods every 28 days for 2 years. For last 1½ years pe- riods lasting 2 to 3 weeks with 2 to 3 week interval	No biopsy	*E.G.H. 600 R.U. & C.G.H. 1500 R.U. in 3 doses alt. days while flowing, then Testosterone Propi- onate 6 c.c., in 3 doses alt. days Then *E.G.H. 2400 R.U. & C.G.H. 3000 R.U. in 6 doses alt. days	Still flowing 2 weeks later and more pro- fusely Still flowing 2 weeks later and more pro- fusely Flow ceased for 2 weeks after 3 injections No evidence of ovula- tion

TABLE III—CONT'D

PATIENT	AGE	MARITAL STATUS	CHIEF COMPLAINT	PHYSICAL ABNORMALITIES AND OPERATIONS	BIOPSY MENSTRUAL HABIT	THYROID	HORMONE THERAPY	RESULTS	BIOPSY
U1866	30	Married 3 yr.	Amenorrhea	Obese Hypoplasia of genital organs Hirsutism B.M.R. -8	Last period 3 years ago Biopsy: Hypoplasia	3 gr. daily	E. G. H. 1200 R.U. in 5 daily doses E. G. H. 1200 R.U. in 5 daily doses Stilbestrol 0.1 mg. daily × 14 Then E.G.H. 1600 R.U. in 4 daily doses followed by E.G.H. 2000 R.U. and C.G.H. 2500 R.U. in 5 doses alt. days	No flow No flow No flow No evidence of ovulation	Refused
U2848	28	Married 7 yr.	Amenorrhea 1932 abortion 3 mo. 1934, normal delivery, term	Obese B.M.R. +1	For 4 yr. occasional period. Last period 3 months ago (1st in 14 mo.) Biopsy: Atrophy or Hypoplasia	2 gr. daily	*E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 3600 R.U. in 6 doses alt. days	No flow No evidence of ovulation	
1036	25	Married 2½ yr.	Amenorrhea	Hypoplasia of genital organs 1938 D. & C. B.M.R. +5	Regular periods till 6 yr. ago. D. & C. in 1938 with 1 period 2 mo. later No biopsy	1 gr. daily	Stilbestrol 1 mg. daily for 5 months Then E.G.H. 1200 R.U. in 3 doses alt. days	No flow No evidence of ovulation	
2175	24	Married 2 yr.	Amenorrhea	Negative B.M.R. -20 to -7	No period in 2½ yr. Biopsy: None	1½ gr. daily	E.G.H. 1000 R.U. in 4 doses alt. days E.G.H. 1200 R.U. in 3 doses 8th-10th days followed by E.G.H. 1200 R.U. and C.G.H. 3000 R.U. in 3 doses 11th-13th days	Periods began 3 months later (2 months after beginning thyroid) every 33-36 days Period every 24 days & ovulation	later—9 months Prolif. End.

U2846	22 S	Amen-orrhea Negative B.M.R. -8	One period at age of 18 Biopsy: Proliferative endometrium with dysplasia	$\frac{3}{4}$ gr. daily *E.G.H. 1600 R.U. in 8 doses twice weekly Then *E.G.H. 1600 R.U. in 8 doses 1 time weekly *E.G.H. 1200 R.U. in 6 daily doses E.G.H. 2000 R.U. in 10 daily doses followed by E.G.H. 2500 R.U. and C.G.H. 5000 R.U. in 10 daily doses E.G.H. 1200 R.U. in 5 daily doses E.G.H. 2200 R.U. in 5 daily doses	Flowed 5 days during last week of injec- tions No flow No flow No flow No evidence of ovula- tion	Prolif. End.
U1805	Mar- ried 10 yr.	Amen-orrhea Obese Hypoplasia of genital organs 1927 Appendec- tomy B.M.R. +15	Always irregular. For 5 years, no periods but occasional stain- ing Biopsy: Hypoplasia	1 gr. daily *E.G.H. 1200 R.U. in 5 doses 6th- 10th days Stilbestrol 1 mg. daily x 14 followed by E.G.H. 1200 R.U. in 5 doses 8th- 12th days	No flow No evidence of ovula- tion No flow No evidence of ovula- tion No flow No evidence of ovula- tion	Hypoplastic Prolif. End. 1, 3, and 5 weeks later —Prolif. End.
U1747	Mar- ried 2 yr.	Amen-orrhea Hypoplasia of genital organs B.M.R. -1	Very irregular. No period in 4 months Biopsy: Proliferative endometrium with hypoplasia			
U1692	Mar- ried 2 yr.	Amen-orrhea Obese	For past 2 years pe- riods scanty and about every 3 months No biopsy			
U1691	Mar- ried 9 yr.	Hypoplasia of genital organs Moderately hirsute 1934 Appendec- tomy B.M.R. +8	Regular periods until one year ago. One period in past year Biopsy: Insufficient tissue obtainable	Stilbestrol .1 mg. daily x 15. Then E.G.H. 1200 R.U. in 5 daily doses E.G.H. 1200 R.U. in 5 daily doses with Stilbestrol .1 mg. daily x 21	Stained 12 days later Flowed 5 days, 1 week after beginning Stilbestrol 28 days later stained months Then amenorrhea 5 months No evidence of ovula- tion No flow	Insufficient tissue No evidence of ovula- tion

proliferative endometrium. Three of the patients received equine gonadotropic hormone alone, and three also received chorionic gonadotropic hormone to act as a luteinizing agent or to aid ovulation synergistically, as recommended by Fluhmann²⁴ and Evans.⁹

The results in this group were uniformly unsatisfactory. One patient, Case U 2875, 14 years of age, after thirty days of alternate flow and cessation of flow following a course of equine gonadotropic hormone and chorionic gonadotropic hormone, developed an amenorrhea which has persisted for three months. Another patient, Case U 142, 16 years of age, had continuous flowing after a course of equine gonadotropic hormone and chorionic gonadotropic hormone. This was followed in two weeks by three injections of testosterone propionate. As there was still no cessation of flow, another course of equine gonadotropic hormone and chorionic gonadotropic hormone was given and the bleeding stopped for two weeks. On resumption of the flow, the skin test was positive for gonadin. In the following six months, two curettages were necessary and showed hyperplasia of the endometrium. Ultimately radium was required to stop the excessive loss of blood. Two patients, Cases U 1863 and U 1797, had a more profuse flow following treatment. One, Case U 1863, required progesterone to arrest the bleeding, and biopsy showed a proliferative endometrium. The other, Case U 1797, received x-ray treatment three months later, and regular periods, average in amount, have continued for a year. Two patients showed no change following therapy.

GROUP III. AMENORRHEA (TABLE III)

This group is composed of 16 patients from 18 to 32 years of age. There were 3 cases of primary amenorrhea, and the duration of amenorrhea in the other patients varied from three months to eight years. Ten of the patients were married and 3 had been pregnant. The basal metabolic rates varied from minus 30 to plus 17. Satisfactory endometrial biopsies were obtained in 9 cases prior to treatment. Seven showed hypoplasia and 2 proliferative endometrium, one with dysplasia. Biopsies were attempted in 3 other cases on one or more occasions, but sufficient tissue could not be obtained. This would indicate hypoplasia. In 4 cases no biopsy was taken. Eleven patients had hypoplasia of the genital organs.

Four patients received equine gonadotropic hormone alone, and the others received either estrogenic or chorionic gonadotropic hormones in addition. The minimum total dosage of equine gonadotropic hormone given in a course of injections was 1,000 R.U. and the maximum, 2,800 R.U. and 2,750 I.U. of equine gonadotropic hormone preparations, in 18 consecutive daily injections. We gave this large dose only very recently to one patient, Case U 1346, because with the recommended dosage our results had been so unsatisfactory. (Frank⁴⁰ and Büttner⁴⁴ consider it justifiable and even necessary to try very high dosages of gonadotropic preparations.) Eight days after the last injection, the patient flowed for five days. Biopsy obtained on the day before flow showed atypical proliferative endometrium, indicating that the patient had not ovulated.

An endometrial biopsy was obtained following each of 16 separate series of equine gonadotropic hormone injections in 9 patients, and in all instances it showed proliferative endometrium, usually with hypoplasia.

Of the 3 cases of primary amenorrhea, one patient flowed for a few days during, and again at the termination of seven months of daily administration of stilbestrol, but with equine gonadotropic hormone alone, there was no flow in any of the 3 cases. Of the 13 cases of secondary amenorrhea, 7 patients were unchanged and 6 had one or more periods of staining or flow, viz., Case U 2846, 22 years of age, had had one period at the age of 18. Prior to therapy she had a proliferative endometrium with dysplasia. While receiving equine gonadotropic hormone in dosages of 200 R.U. by injection, twice weekly, she had a five-day flow. Three later courses of equine gonadotropic hormone, one with large dosage, produced no flow, and a subsequent biopsy showed a proliferative endometrium. Case U 1805, a 28-year-old married woman, had had no periods and only occasional staining for five years. Biopsy before treatment showed hypoplasia. Twenty-five days after a second course of equine gonadotropic hormone she flowed for three days from a hypoplastic endometrium. (This patient was given a three months' vacation and only re-

U1021	34	Mar- ried 9 yr.	Amen- orrhea normal deliv- ery full term	Negative 1939 D. & C. polypectomy B.M.R. -21 to -6	No period since child born 8 yr. ago. Occ. scanty period with intensive therapy with C.G.H., es- trone, pituitary ex- tracts, etc. Biopsy: Hypoplasia	3 gr. daily	*E.G.H. 1000 R.U. in 4 doses alt. days *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days E.G.H. 1600 R.U. in 4 doses alt. days E.G.H. 1600 R.U. in 4 doses alt. days E.G.H. 800 R.U. in 4 doses alt. days followed by E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 1800 R.U. in 3 doses alt. days	Flowed 3 weeks later for 2 days Flowed 1 week later for 5 days Flowed 8 days later for 4 days No flow No flow No flow No evidence of ovula- tion	Flowed 3 weeks later for 2 days Flowed 1 week later for 5 days Flowed 8 days later for 4 days No flow No flow No flow No evidence of ovula- tion	Prolif. End. Hypoplasia Hypoplasia Hypoplasia Hypoplasia Prolif. End. Atypical Prolif. End.
U1346	25	Mar- ried 3 yr.	Amen- orrhea	Hypoplasia of genital organs B.M.R. -2	Irregular for 4-5 yr. 3 periods in past year. Last period 2 months ago. Biopsy: Hypoplasia	3 gr. daily	*E.G.H. 800 R.U. in 4 doses alt. days *E.G.H. 800 R.U. in 4 doses alt. days followed by *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days *E.G.H. 2400 R.U. in 6 doses alt. days and *E.G.H. 2400 R.U. and C.G.H. 3000 R.U. 6 doses alt. days Stilbestrol 1 mg. daily x 21 Then E.G.H. 1200 R.U. in 4 doses 6th-9th days followed by E.G.H. 1200 R.U. and C.G.H. 4000 R.U. in 4 doses 10th-13th days E.G.H. 2750 I.U. in 11 daily doses followed by E.G.H. 2800 R.U. and C.G.H. 7000 R.U. in 7 daily doses.	No flow No flow Stained 4 days after last injection Followed by bleeding 4 days No flow 8 days later flowed for 5 days No evidence of ovula- tion	No flow No flow Stained 4 days after last injection Followed by bleeding 4 days No flow 8 days later flowed for 5 days No evidence of ovula- tion	Hypoplasia Hypoplasia Hypoplasia Hypoplasia Prolif. End. Atypical Prolif. End.

tropic hormone. One other, an anovulatory patient, was found by biopsy to be ovulating four months after treatment. One patient with dysfunctional bleeding continued to flow for a month following equine gonadotropic hormone therapy and since then has had amenorrhea for three months. Six patients with amenorrhea stained or flowed after treatment, but none of these showed evidence of ovulation. Only one patient continued to flow at regular intervals. She seemed to be responding rather to thyroid than to equine gonadotropic hormone stimulation.

6. Allergic reactions to equine gonadotropic hormone appeared in 3 patients following therapy, and in 3 patients, a cyst of the ovary was noted following treatment.

CONCLUSION

With the varying dosages used in this study, the equine gonadotropic hormone has not been shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea, nor has it had any apparent effect in cases of sterility. Three cases of cysts of the ovary were noted following therapy. Although we cannot, and do not, attribute them to equine gonadotropic hormone, we cannot deny the possibility that the treatment may have been instrumental in causing the condition. We believe that a great deal of clinical experimentation is necessary before the value of this hormone will be established.

We are deeply indebted to the Cutter Laboratories, the Schering Corporation, the Winthrop Chemical Company, the Squibb Company, Merck and Company, and Reed and Carnrick for the materials used in this study.

REFERENCES

- (1) Zondek, B., and Aschheim, S.: *Klin. Wehnschr.* 6: 248, 1927. (2) Smith, P. E., and Engle, E. T.: *Am. J. Anat.* 40: 159, 1927. (3) Fevold, H. L., Hisaw, F. L., and Leonard, S. L.: *Am. J. Physiol.* 97: 291, 1931. (4) Fevold, H. L., Hisaw, F. L., Hellbaum, A., and Hertz, R.: *Ibid.* 104: 710, 1933. (5) Hisaw, F. L., Hertz, R., Hellbaum, A., and Fevold, H. L.: *Proc. Soc. Exper. Biol. & Med.* 30: 39, 1932. (6) Aschheim, S., and Zondek, B.: *Klin. Wehnschr.* 7: 1404, 1928. (7) Gray, L. A.: *South. M. J.* 33: 160, 1940. (8) Engle, E. T.: *Proc. Soc. Exper. Biol. & Med.* 30: 530, 1933. (9) Evans, H. M.: *West. J. Surg.* 44: 175, 1936. (10) Fevold, H. L., and Hisaw, F. L.: *Am. J. Physiol.* 109: 655, 1934. (11) Foster, M. A., and Hisaw, F. L.: *Anat. Rec.* 62: 75, 1935. (12) Engle, E. T.: *J. A. M. A.* 93: 276, 1929. (13) Johnson, C. E.: *Am. J. OBST. & GYNEC.* 29: 120, 1935. (14) Foster, M. A., and Fevold, H. L.: *Am. J. Physiol.* 121: 625, 1938. (15) Adair, F. L.: *Obstetrics and Gynecology*, Philadelphia, 1940, Lea & Febiger. (16) Henderson, D. N.: *Canad. M. A. J.* 32: 615, 1935. (17) Geist, S. H.: *Am. J. OBST. & GYNEC.* 26: 588, 1933. (18) Geist, S. H.: *Proc. Soc. Exper. Biol. & Med.* 31: 434, 1934. (19) Hamblen, E. C.: *Endocrinology* 19: 169, 1935. (20) Rock, J., and Bartlett, M. K.: *Am. J. OBST. & GYNEC.* 31: 634, 1936. (21) Sevringhaus, E. L.: *Bull. New York Acad. Med.* 16: 53, 1940. (22) Novak, E.: *Am. J. OBST. & GYNEC.* 37: 605, 1939. (23) Siegler, S. L., and Fein, M. J.: *Ibid.* 38: 1021, 1939. (24) Fluhmann, C. F.: *Menstrual Disorders*, Philadelphia, 1939, W. B. Saunders Co. (25) Hamblen, E. C.: *J. A. M. A.* 108: 100, 1937. (26) Payne, S. A., and Shelton, E. K.: *Endocrinology* 23: 598, 1938. (27) Hamblen, E. C.: *Am. J. Surg.* 41: 35, 1938. (28) Stein, I. F., and Cohen, M. R.: *Am. J. OBST. & GYNEC.* 38: 465, 1939. (29) Cole, H. H., and Hart, G. H.: *Am. J. Physiol.* 93: 57, 1930. (30) Goss, H., and Cole, H. H.: *Endocrinology* 15: 214, 1931. (31) Fleischer, G., Schwenk, E., and Meyer, K.: *Nature*, London 142: 835, 1938. (32) Cole, H. H., Guilbert, H. R., and Goss, H.: *Am. J. Physiol.* 102: 227, 1932. (33) Cole, H. H., and Miller, R. F.: *Ibid.* 104: 165, 1933. (34) Catchpole, H. R., and Lyons, W. R.: *Am. J. Anat.* 55: 167, 1934. (35) Cole, H. H., and Saunders, F. J.: *Endocrinology* 19: 199, 1935. (36) Cole, H. H.: *Am. J. Anat.* 59: 299, 1936. (37) Idem: *Am. J.*

cently returned to the clinic to say that she had had a period during each of the three months. It is possible that these periods were ovulatory in character, but spontaneous return of the menses is not rare in secondary amenorrhea. Frank⁴⁰ cites 7 cases of amenorrhea, one of 17 years' duration, in which menstruation returned during a study period prior to treatment.) In one patient (U 1692), there was staining on two occasions after courses of equine gonadotropic hormone, but when last seen, the patient reported no traces of menstruation for five months. The patient in Case U 1346 stained for four days after a course of equine gonadotropic hormone and chorionic gonadotropic hormone, and flowed for five days after a very large dose of equine gonadotropic hormone followed by equine gonadotropic hormone combined with chorionic gonadotropic hormone. In both instances flow was from a proliferative endometrium which in one instance showed hypoplasia. The patient in Case U 1021, a 34-year-old woman who had not flowed in the eight years following the birth of a child, had three periods of flow: Two following equine gonadotropic hormone injections alone and one after administration of a course of equine gonadotropic hormone and chorionic gonadotropic hormone. Twice, flow was from a proliferative endometrium, one with hypoplasia. Another biopsy, two months later, also showed hypoplasia. Patient, Case 2175, was 24 years of age and had had no period in two and one-half years. No biopsy was obtained prior to treatment. The basal metabolic rate was minus 20. One course of equine gonadotropic hormone produced no results. Thyroid was given, and two months later the patient began to flow every thirty-three to thirty-six days. Biopsy showed a proliferative endometrium, so a course of equine gonadotropic hormone combined with chorionic gonadotropic hormone was given. The next three periods were about twenty-four days apart. No biopsy was obtained to prove ovulation nor has the patient become pregnant in the past year. The low basal metabolic rate which was corrected by thyroid seems to us to be the probable cause of the irregularity.

In one patient in this group, a cyst of the ovary appeared following equine gonadotropic hormone therapy. The patient in Case U 2848, 28 years of age, had a full-term child in 1934. Since then she has had an occasional period, but only one in the seventeen months prior to treatment. There was no flow following a course of equine gonadotropic hormone combined with chorionic gonadotropic hormone, and another course of equine gonadotropic hormone alone. One week following treatment, examination showed no signs of a cyst, but two months later, with no treatment in the interim, a cyst was palpated and was ruptured at examination. Sixteen days later, the patient began to flow and the period in the next month was proved to be from a secretory endometrium. She has not become pregnant in nine months, but her periods have continued to be regular.

SUMMARY

1. A gonadotropic substance obtained from the serum of pregnant mares has stimulated ovulation in immature laboratory animals.
2. It is reported to have produced ovulation and multiple ovulation in both the normal and abnormal human ovary, with gratifying results in cases of sterility, dysfunctional flow, and amenorrhea.
3. This study deals with a series of 48 cases of sterility, dysfunctional flowing, and amenorrhea treated with equine gonadotropic hormone. Sixteen patients were not ovulating, as proved by endometrial biopsy, and 9 others clinically were not ovulating. Twenty patients were ovulating, as shown by biopsy, and 3 were clinically ovulating. Effects of treatment were judged in 12 cases by endometrial biopsy and by subsequent clinical course in the others.
4. Thirty-nine patients (81.2 per cent) were apparently unaffected by equine gonadotropic hormone.
5. In no case was there any definite evidence of stimulation of ovulation by equine gonadotropic hormone. In the sterility group there was one pregnancy, but we feel it cannot be attributed to equine gonado-

EXPERIMENTAL DATA

To test the estrogenic effect of pregnenolone, 5 mature female rats, previously castrated, were fed 10 mg. of the drug on each of two consecutive days. Daily vaginal smears showed complete estrus occurring on the fourth day. Thus pregnenolone shows a qualitative estrogenic action.

To determine the androgenic effects, 3 male rats, aged 2 months, were castrated and fed pregnenolone, 1 mg. daily for ten days, a total of 10 mg. This small dose did not prevent castration changes in the seminal vesicles. However, when 3 male rats, aged two months, were castrated and fed pregnenolone, 2.5 mg. daily for ten days, a total of 25 mg., slight secretory activity occurred in 2 and marked secretory activity was present in the seminal vesicles of the third animal. Two male rats, aged 2 months, fed 5 mg. daily for ten days, showed a more marked androgenic effect. There was marked secretory activity in one, and moderate secretory activity in the seminal vesicles of the second rat. Thus, pregnenolone prevented castration changes in the young male rats when given orally in doses of 25 to 50 mg.

To determine the progestational effect, pseudopregnancy was produced according to the method of Astwood:⁴ Mature female rats in full estrus were given faradic stimulation to the cervix. Four days later, the animals were castrated and the endometrium of one uterine horn traumatized with a needle. Ten milligrams of pregnenolone was mixed with their food daily for five days, a total of 50 mg. The animals were then killed and the uteri examined for the presence of deciduomas, with the following results:

Controls	J	Non-castrate	4 plus reaction
	K	Castrate	No reaction
19		Castrate plus 50 mg. pregnenolone	4 plus reaction
22		Castrate plus 50 mg. pregnenolone	4 plus reaction
2		Castrate plus 50 mg. pregnenolone	3 plus reaction
19A		Castrate plus 50 mg. pregnenolone	1 plus reaction
9		Castrate plus 50 mg. pregnenolone	1 plus reaction

Thus, 3 out of 5 animals showed strongly positive and the other 2 weakly positive results.

These experiments confirm the work of Emmens and Parkes,⁵ who first described the multiple activities of anhydro-oxy-progesterone (pregnenolone). The androgenic properties which we obtained with this product are comparable to those which Greene, Burrell and Ivy³ obtained with progesterone.

TABLE I. ORAL PREGNENOLONE IN THE MATURE RAT

NO. OF ANIMALS	DAILY DOSE MG.	NO. OF DAYS	TOTAL DOSE MG.	OVARIAN WEIGHT MG.	UTERINE WEIGHT MG.
8	0.25	20	5	Av. 48	Av. 320
3	1.0	20	20	<div> <div>26</div> <div>36</div> <div>50</div> <div>28</div> <div>32</div> <div>26</div> <div>50</div> </div>	<div> <div>Av. 280</div> <div>216</div> <div>340</div> <div>180</div> <div>380</div> </div>
4	5.0	20	100	<div> <div>Av. 48</div> <div>Av. 44</div> <div>Av. 42</div> </div>	<div> <div>Av. 260</div> <div>Av. 240</div> <div>Av. 420</div> </div>
6	0.5	60	30	Av. 48	Av. 260
7	1.0	60	60	Av. 44	Av. 240
5	2.0	60	120	Av. 42	Av. 420
Controls			Colony	Av. 84	Av. 340

The effect of oral pregnenolone in the intact adult rat* is shown in Table I. A series of 33 normal mature female rats were fed pregnenolone in dosages varying from 0.25 mg. to 5 mg. daily for twenty days in one series and for sixty

*With the assistance of Dr. Charles Freed.

Physiol. 119: 704, 1937. (38) *Hartman, C. G.*: Bull. Johns Hopkins Hosp. 63: 351, 1938. (39) *Bowes, K.*: Brit. M. J. 2: 904, 1937. (40) *Frank, R. T., et al.*: J. A. M. A. 109: 1863, 1937. (41) *Watson, B. P., Smith, P. E., and Kurzrok, R.*: AM. J. OBST. & GYNEC. 36: 562, 1938. (42) *Davis, M. E., and Koff, A. J.*: AM. J. OBST. & GYNEC. 36: 183, 1938. (43) *Hamblen, E. C.*: Endocrinology 24: 848, 1939. (44) *Büttner, W.*: Arch. f. Gynäk. 163: 487, 1937. (45) *Hamblen, E. C.*: Endocrinology 24: 13, 1939. (46) *Campbell, R. E., and Sevringhaus, E. L.*: AM. J. OBST. & GYNEC. 37: 913, 1939. (47) *Kennedy, R. B., and Shelton, C. F.*: J. Michigan M. Soc. 38: 209, 1939. (48) *Hall, G. J.*: California & West. Med. 51: 159, 1939. (49) *Hawkinson, L. F.*: Ibid. 51: 162, 1939. (50) *Rubenstein, B. B.*: Ohio State M. J. 35: 1066, 1939. (51) *Sevringhaus, E. L., and Campbell, R. E.*: Am. J. Surg. 48: 197, 1940. (52) *Hart, G. H., and Cole, H. H.*: Proc. Am. Soc. Animal Product., 1933. (53) *Fluhmann, C. F.*: AM. J. OBST. & GYNEC. 28: 668, 1934. (54) *Rock, J., Bartlett, M. K., and Matson, D. D.*: Ibid. 37: 3, 1939. (55) *Hartman, C. G.*: Ibid. 26: 600, 1933.

LABORATORY AND CLINICAL EXPERIENCE WITH ORAL PREGNENINOLONE*

MELVIN R. COHEN, M.D., AND IRVING F. STEIN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and the Samuel A. Deutsch Serum Center, Research Department, Michael Reese Hospital)

UNTIL recently, practically the only orally active hormone was thyroid extract. Although many glandular extracts and residues have been exploited commercially, with few exceptions they have proved to be ineffectual when given by mouth.

Inhoffen and Hohlweg¹ (1938) described two very potent orally active synthetic hormones; 17 Aethinyl Oestradiol, and Pregnen-in-20-on-3-ol 17 (ethinyl testosterone); the first, a potent estrogenic substance, was subsequently discarded because of its accompanying side effects. The second, a progestational substance designated in this report as pregnenolone,[†] was found by them to produce a positive response in infantile rabbits after the administration of but 4 mg. orally. This preliminary report was augmented by the results of other investigators.^{2,5} Clauberg and Ustün⁷ observed the action of pregnenolone in the human being; they showed that bleeding associated with glandular cystic hyperplasia could be controlled and the endometrium transformed to a pseudodecidua by the use of proluton "C."[‡] Subsequently, it was found that progestational effects could also be produced by oral pregnenolone in postmenopausal women. Zondek and Rozin¹⁰ found that the effects of oral pregnenolone in the human female were similar to those produced by progesterone hypodermically. Recently, Hamblen and others¹³ reported the oral effectiveness of pregnenolone in the treatment of 7 patients with menometrorrhagia. In their study, no alteration in urinary pregnanediol or androgen titer was found.

In order to evaluate this new oral progesterone-like substance, we planned a laboratory and clinical investigation. We first studied the effects of this drug upon the rat in order to coordinate its multiple hormonal action, to observe its effects upon the intact pregnant animal, and to test for toxicity with reference to effects upon the liver and kidney. Clinically, we used the preparation chiefly in those patients who presented a menometrorrhagia. In addition, we used it in some patients complaining of dysmenorrhea, amenorrhea, premenstrual tension, and mazoplasia.

*Presented at a meeting of the Chicago Gynecological Society, May 17, 1940.

†Also known as anhydro-oxy-progesterone, Pregneninonol.

‡A brand of pregnenolone.

TABLE III. ORAL PREGNENINOLONE TOXICITY EXPERIMENT (RATS)

NO.	KIND	DAILY DOSE MG.	TOTAL DOSE MG.	LIVER	KIDNEY	REMARKS
26	2 Mo. male	0	0	Cloudy swelling	Normal	Control
28	Castrate male	5	50	Normal	Cloudy swelling	
29	Castrate male	5	50	Cloudy swelling Hyperemia	Cloudy swelling Hyperemia	
30	2 Mo. male	2.5	25	Cloudy swelling	Early focal necrosis	
31	Castrate male	2.5	25	Cloudy swelling	Early focal necrosis	
32	Castrate male	2.5	25	Cloudy swelling Hyperemia	Cloudy swelling	
33	Mature female	5	55	Cloudy swelling Hyperemia	Cloudy swelling Hyperemia	Miscarriage
34	Mated Mature female	5	55	Cloudy swelling	Cloudy swelling Hyperemia	Miscarriage
45	Mated Anestrus	1	6	Cloudy swelling Hyperemia	Cloudy swelling Hyperemia	
46	Pregnant	1	6	Cloudy swelling Hyperemia	Early focal necrosis	Miscarriage
3	Mature Pregnant	5	195	Cloudy swelling	Diffuse necrosis	5 normal; 1 stillborn
5	Mature Pregnant	5	180	Cloudy swelling Hyperemia		4 normal; mother died
8	Mature Pregnant	5	200	Cloudy swelling Hyperemia	Focal necrosis	11 normal
9	Mature Pregnant	5	135	Cloudy swelling Hyperemia	Diffuse necrosis	Miscarriage after 20 mg.
11	Mature Pregnant	5	180	Cloudy swelling Hyperemia		8 normal; mother died
10	Mature Pregnant	1	39	Cloudy swelling Hyperemia	Cloudy swelling	8 normal
12	Mature Pregnant	1	31	Cloudy swelling Hyperemia	Focal necrosis	6 normal; 3 stillborn
13	Mature Pregnant	1	28	Cloudy swelling Hyperemia	Focal necrosis	Anestrus
17	Mature Pregnant	1	39	Cloudy swelling Hyperemia	Specimen lost	8 normal
20	Mature Pregnant	1	28	Cloudy swelling Hyperemia	Diffuse necrosis	11 normal
114	Mature Pregnant	0	0	Cloudy swelling	Slight cloudy Swelling	Control

pale and coarsely granular. The individual cell outlines are indistinct. The nuclei in many areas are hyperchromatic but stain distinctly throughout. The sinusoids and central veins are markedly engorged with red blood cells. Thus, cloudy swelling and hyperemia are present in the liver. However, cloudy swelling of the liver was frequently present in the control group and microscopic section differs only in the absence of marked hyperemia, a distinguishing feature in the pregnenolone rats. The kidneys show more significant changes. In 3 of our pregnant animals, a severe diffuse tubular necrosis is present. Four other pregnant rats show an early focal necrosis of the tubules. Two nonpregnant rats show an early focal tubular necrosis also, while the remainder all show a severe cloudy

days in the other. The influence upon the uterine and ovarian weights was noted. In all instances, the ovarian weights were markedly reduced even to the point of extreme atrophy in some cases. There was less effect upon the uterus in that the uterine weight was unaffected or decreased in all with the exception of the series which received the largest dose (2 mg. for sixty days: total, 120 mg.). This dose produced a definitely increased uterine weight response well above the normal controls. These results show that pregnenolone inhibits the gonadotropic action of the anterior pituitary gland in intact mature female rats. Pregnenolone in large doses (120 mg.) produced a positive uterine weight response in the presence of ovarian suppression.

To determine the effect of oral pregnenolone on the *intact pregnant rat*, mature rats were mated and daily vaginal smears obtained. The onset of pregnancy was determined by the last estrus, the vaginal plug, and/or microscopic evidence of spermatozoa. Beginning with the fifth day of pregnancy, pregnenolone was fed to animals over a period of six to forty days with a total dosage of from 6 to 200 mg. The effects upon pregnancy and lactation were noted (Table II). It was

TABLE II. PREGNENINOLONE ORALLY IN PREGNANCY (RATS)

NO.	LAST ESTRUS OR SPERM	DELIV- ERY	DURATION OF PREGNANCY DAYS	DAILY DOSE	TOTAL DOSE	LITTER	REMARKS
33	4/27/39		11	5	55	0	Bleeding, 5/7/39; aborted
34	4/29/39		8	5	55	0	Sperm recovered: no pregnancy
3	9/4/39	9/26/39	22	5	195	5 Alive 1 Still-born	Young died
5	9/1/39	9/23/39	22	5	180	4 Alive	Mother and 2 offspring died
8	9/4/39	9/27/39	23	5	200	11 Alive	1 offspring survived
9	9/5/39		8	5	135	0	Bleeding, 9/12/39; lap. pregnant
11	9/1/39	9/23/39	22	5	180	8 Alive	Mother and 4 offspring died
10	9/4/39	9/25/39	21	1	39	8 Alive	Young died
12	9/3/39	9/26/39	23	1	31	6 Alive 3 Still-born	2 offspring survived
17	9/5/39	9/27/39	22	1	39	8 Alive	3 offspring survived
20	9/1/39	9/22/39	21	1	28	11 Alive	Young died
3A	7/7/39	7/29/39	22	1	6	10 Alive	Lactation unimpaired
10A	7/7/39	7/29/39	22	1	6	7 Alive	Lactation unimpaired
15	7/10/39		9	1	6	0	Bleeding, 7/19/39; aborted

found that abortion occurred in 3 of 14 animals and stillbirths occurred after 2 matings. Lactation was definitely impaired in almost all, and very few of the offspring survived. Two of the mothers died after ingesting 180 mg. of pregnenolone each. In this series, there was no appreciable increase in the duration of pregnancy. On the other hand, Courrier and Jost⁶ found that pregnenolone maintained pregnancy in *spayed* rabbits when given combined orally and hypodermically. Although pregnenolone may maintain pregnancy in the *spayed* rabbit, it showed certain deleterious effects upon the intact pregnant rats in our series. The effect upon lactation is not surprising inasmuch as progesterone, estrogens, and androgens will all inhibit lactation, and pregnenolone exhibits all of these hormonal actions.

Sections of the liver and kidney were examined at the conclusion of the above experiments to determine *toxicity* of the drug, and the findings were tabulated (Table III). Grossly, the liver and kidney of the rats fed pregnenolone differ little from the normal controls except for marked congestion. Histologic section of the liver (Fig. 1) shows the cords markedly swollen and the cytoplasm of the liver cells

the lumina of the tubules contain a pale pinkish structureless material. The capillaries of the glomeruli and of the interstitial tissues are markedly engorged with erythrocytes.

Focal Necrosis of the Kidney.—Cloudy swelling as above. Scattered throughout the cortex occasional groups of tubules are found, the architecture of which is indistinct or occasionally almost completely destroyed. These tubules are shadowy in outline and they are filled with a pale eosinophilic amorphous material. The cell outlines cannot be distinguished and the nuclei stain poorly or not at all. The lumina of these tubules contain a fibrillar structureless pink-staining material. Such tubules are found scattered throughout, interspersed with those described above. In these areas are seen occasional extravasations of red blood cells.

Diffuse Tubular Necrosis (Figs. 3 and 4).—In many areas, the renal architecture is barely recognizable, only ghostlike, poorly defined outlines of tubules being discernible. The finer histologic details of these tubules are completely obliterated. The lining cells cannot be distinguished, their nuclei do not stain at all and the lumina are filled with a pale eosinophilic structureless debris. The cell outlines cannot be discerned at all. These changes are seen most prominently in the convoluted tubules and the changes are scattered diffusely in sections taken from the renal cortex. Interspersed with these necrotic tubules are occasional small tubules, the architecture of which is in a better state of preservation. Their lining cells are fairly clearly demarcated and the nuclei stain distinctly; however, the cytoplasm is pale, coarsely granular, and the individual cells are swollen, bulging into the lumen, causing almost complete obliteration of the latter. The capillary tufts of the glomeruli in some areas are rather shrunken, and in others hyperemic, and in many of the glomeruli, pale, amorphous eosinophilic material is found within the space between the capillary tuft and Bowman's capsule. The blood vessels of the interstitial tissue are markedly engorged with red blood cells.

No histologic sections were taken on animals found dead in their cages, as we did not wish to confuse our findings with post-mortem changes. In summary, the most characteristic changes were present in the kidneys; tubular necrosis was extensively present in the kidneys of the pregnant rats fed pregnenolone in large amounts.

CLINICAL USE OF PREGNENINOLONE

Oral pregnenolone was prescribed for 37 patients complaining of menometrorrhagia, dysmenorrhea, premenstrual tension, amenorrhea and mazoplasia. The drug was administered orally in daily amounts varying from 15 to 30 mg.; the total dosage was limited to 300 mg. during any one month. We endeavored to prescribe it seven to ten days premenstrually which at times was difficult inasmuch as menstrual cycles were extremely variable in the group under study and the drug frequently delayed the following period. Frequently, the treatment was prescribed during an active bleeding phase.

Of the 29 patients with menometrorrhagia, 4 upon further study and laparotomy were found to have definite anatomic changes. Small fibroids were present in 2, bilateral polycystic ovaries in 1, and chronic salpingo-oophoritis in the remaining 1. One patient in whom the small fibroids were present responded temporarily to pregnenolone. Improvement was noted in 12, or 48 per cent, of 25 patients complaining of essential menometrorrhagia. This improvement was temporary unless treatment was continued for several months. A few patients reported diminution in quantity of the flow but complained of increased duration with intermenstrual spotting. The following case reports are of interest:

Miss L. B., aged 23 years, single, menses began at 13 years, regular, 28-day cycles, 3 days' duration, moderate flow, no pain. *Complaint:* Menorrhagia, of two months' duration. The last 2 periods were very profuse, lasting four to seven

swelling. A few of our control group showed slight cloudy swelling of the kidney, but never necrosis. The changes in these kidneys are described in detail below.

Marked Cloudy Swelling; Hyperemia of the Kidney (Fig. 2).—The cells lining the tubules are markedly swollen and their cytoplasm is pale eosinophilic and coarsely granular; the cell outlines are indistinct. The lumina of the tubules in many areas are almost completely obliterated by the markedly swollen lining cells. Occasionally,

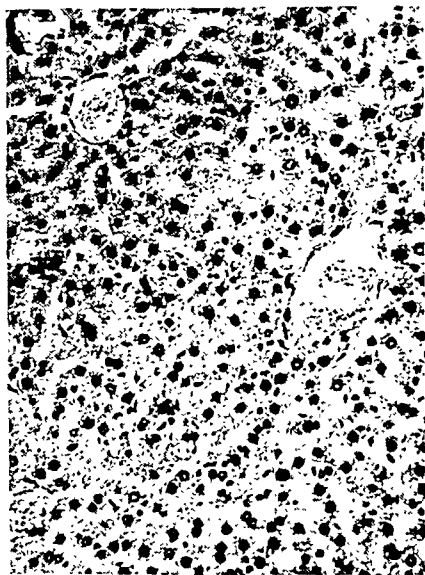


Fig. 1.

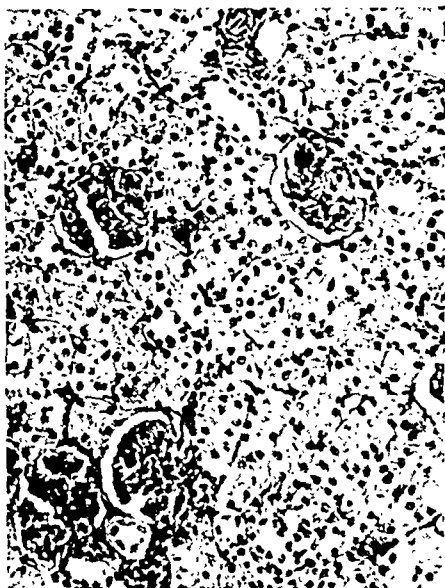


Fig. 2.

Fig. 1.—Liver of Rat 32. After 25 mg. of pregneninolone orally. Note severe cloudy swelling and marked engorgement of central veins and sinusoids. (X210.)

Fig. 2.—Kidney of Rat 45. After 6 mg. of pregneninolone orally. Note severe cloudy swelling. Glomeruli show no changes. (X190.)



Fig. 3.

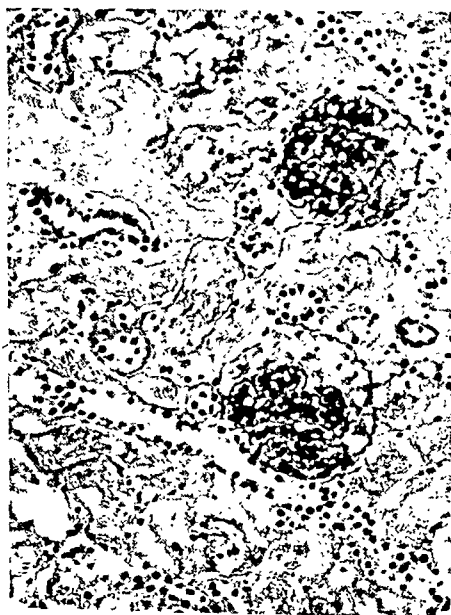


Fig. 4.

Fig. 3.—Kidney of Rat 20 after 28 mg. of pregneninolone orally in pregnancy. Severe diffuse necrosis of tubules. Note exudate in glomeruli and hemorrhage in interstitial tissue. (X170.)

Fig. 4.—Kidney of Rat 9 after 135 mg. of pregneninolone orally in pregnancy. Note severe diffuse tubular necrosis and glomerular exudate. (X180.)

G. B., aged 36 years. *Complaint:* Menorrhagia of six months' duration. Periods were regular, with 28-day cycles, four to five days' duration and profuse flow. Endometrial biopsies taken on the fourteenth and seventeenth days of two different cycles showed a proliferating phase. Pregneninolone, 30 mg. daily, was given during the second half of the cycle and produced a delayed period with moderate flow. Endometrial biopsy (premenstrual) showed a late secretory phase. Treatment during two following cycles was also followed by a moderate flow. Recurrence of menorrhagia followed cessation of treatment. No side reactions were reported.

E. H., aged 28 years. *Complaint:* Menorrhagia and dysmenorrhea since onset of menses at age of 15. Periods were regular, every twenty-eight days, lasting fourteen days; they were profuse and accompanied by clots. Biopsy taken on the twenty-fourth day of the cycle revealed polypoid hyperplastic endometrium. After treatment for one week with 30 mg. daily of pregnenolone, biopsy showed a polypoid edematous secretory endometrium with cystic changes (Figs. 5 and 6). Her period began the day biopsy was taken and continued profusely for fifteen days. Headache accompanied ingestion of the drug. Dysmenorrhea as before.

Pregneninolone was of little benefit for the relief of dysmenorrhea in the dosage employed. Of 10 patients treated, only 3 reported improvement, while 2 complained of intensification of pain. One patient, completely relieved by previous testosterone propionate (perandren) therapy, reported only slight improvement with pregnenolone. A small miscellaneous group of patients with premenstrual tension, secondary amenorrhea and mastoplasia showed some temporary benefit (Table IV).

TABLE IV. CLINICAL RESULTS

NUMBER	COMPLAINT	IMPROVED	PERCENTAGE
25	Essential menometrorrhagia	12	48.0
10	Dysmenorrhea	3	30.0
2	Premenstrual tension	2	
1	Secondary amenorrhea	1	
1	Mastoplasia	1	
37	—Total number of patients		

It is characteristic of patients with functional menometrorrhagia that any endometrial pattern may be found on biopsy. In our series, the usual pattern was an early secretory phase before treatment which changed to a pseudodecidua following therapy. The biopsies of 2 patients complaining of menometrorrhagia showed persistent proliferative endometria; there was transformation in one case (Figs. 5 and 6). These endometrial studies are of little significance in demonstrating progestational activity in the human being during reproductive life. However, in postmenopausal women, Salmon, Walter and Geist¹¹ were able to produce progestational effects with pregnenolone after priming with estradiol benzoate, and the work of Wenner and Joel¹² confirmed their findings.

Side reactions incident to the use of this drug were frequent but rather mild (Table V). Fifteen patients, or 31 per cent of the total group, complained of nausea, vomiting, abdominal pain, weakness and dizziness, or severe headache. These reactions were more frequently observed when larger doses of pregnenolone (30 mg. daily) were

days and accompanied by marked weakness. Rectal examination disclosed a normal uterus; the left ovary was tender. The patient was given pregnenolone, 30 mg. daily, beginning on the twenty-sixth day of the cycle. Medication was stopped after three days because the patient complained of nausea and abdominal cramps. The next menstrual period was more profuse and was accompanied by severe dysmenorrhea. Subsequent laparotomy for acute appendicitis revealed polycystic ovaries.

This illustrates the difficulty in differentiating true essential menorrhagia from undiagnosed pathologic changes. This patient's symptoms were aggravated with pregnenolone. It is possible that painless anovulatory bleeding associated with bilateral polycystic ovaries was changed to painful menstruation after the use of oral pregnenolone.

R. G., aged 27 years. *Complaint:* Late puerperal metrorrhagia, six weeks post partum, lasting 10 days. No response to prolan therapy. Pregnenolone, 15 mg. daily was given, with cessation of the flow on the third day. Nausea lasting several hours was noted as a side reaction and vomiting occurred once. There was no recurrence of bleeding.



Fig. 5.



Fig. 6.

Fig. 5.—Persistent proliferative phase before treatment. ($\times 76$.)

Fig. 6.—Late secretory phase after oral pregnenolone. ($\times 72$.)

M. L., aged 30 years. Menses: onset at 13 years of age, regular 24-day cycles until five months ago, five to six days' duration, profuse flow. A left oophorectomy (simple cyst) was performed for intractable metrorrhagia of five months' duration; the metrorrhagia continued. Endometrial biopsy revealed an early secretory phase; pelvic pneumogram revealed normal-sized uterus and ovary. Pregnenolone, 30 mg. daily, produced nausea during the first day. Bleeding stopped abruptly but returned. Pregnenolone, 30 mg. daily, produced severe nausea. Irregular bleeding is still present despite a late secretory phase after pregnenolone therapy.

L. J., aged 31 years. *Complaint:* Menorrhagia of four to five months' duration, periods occurring every twenty-one to twenty-four days, five to six days' duration, and of profuse flow. Pregnenolone, 15 mg. daily, for seventeen days, beginning the seventh day of the cycle. The subsequent period was delayed one week, lasted for six days, was profuse in amount but less painful. The dose was repeated the following month; the next period was one week late, scant, and lasted three days. The patient has been followed for one year, and there has been no recurrence of menorrhagia. No side reactions were noted.

strated in rats (chiefly in pregnancy) after administration of this preparation and therefore caution must be exercised in its use in the human being. When given to the intact pregnant rat, it produced abortion and stillbirths, and lactation was definitely impaired. In 31 per cent of our cases, the drug produced mild undesirable side effects, but these untoward reactions were seldom so severe as to necessitate withdrawal of the drug. Pregneninolone proved effective in approximately one-half of our patients complaining of menometrorrhagia but proved to be of little benefit in dysmenorrhea.

We gratefully acknowledge our indebtedness to Dr. Ernst Oppenheimer of the Ciba Corporation who generously supplied us with pregnenolone. We also wish to acknowledge our thanks to Drs. Max Appel and Charles Freed for their invaluable aid.

REFERENCES

- (1) *Inhoffen, H. H., and Hohlweg, W.*: *Naturwiss* 26: 96, 1938. (2) *Ruzicka, L., Hofmann, K., and Meldahl, H. F.*: *Helvet. Chim. Acta*. 21: 372, 1938. (3) *Greene, R. R., Burrill, M. W., and Ivy, A. C.*: *Endocrinology* 24: 351, 1939. (4) *Astwood, E. B.*: *J. Endocrinol.* 1: 49, 1939. (5) *Hohlweg, W., and Herloff, H.*: *Klin. Wchnschr.* 18: 77, 1939. (6) *Courrier, R., and Jost, A.*: *Compt. rend. Soc. de Biol. Paris* 130: 1162, 1939. (7) *Clauberg, C., and Üstün, Z.*: *Zentralbl. f. Gynäk.* 62: 1745, 1938. (8) *Emmens, C. W., and Parkes, A. S.*: *Nature* 143: 1064, 1939. (9) *Idem*: *J. Endocrinol.* 1: 323, 1939. (10) *Zondek, B., and Rozin, S.*: *Lancet* 1: 504, 1939. (11) *Salmon, U. J., Walter, R. I., and Geist, S. H.*: *Proc. Soc. Exper. Biol. & Med.* 40: 252, 1939. (12) *Wenner, R., and Joel, K.*: *Lancet* 2: 668, 1939. (13) *Hamblen, E. C., Powell, N. B., Cuyler, K. W., and Pattee, C. J.*: *Endocrinology* 26: 201, 1940.

DISCUSSION

DR. E. S. BURGE.—We have been able to confirm the multiple activities of pregnenolone in the rabbit and white rat. In many other ways our experimental and clinical results were similar to those of Dr. Cohen. I shall discuss only those points at variance.

One must be fully cognizant of the possible toxic properties of any new therapeutic agent. In none of our 51 rats or 19 rabbits, however, was there gross or histologic evidence of damage to the liver, kidneys, or adrenal glands. In an effort to prolong pregnancy in 9 rats, 8 to 120 mg. of pregnenolone was given orally from the eighteenth day of pregnancy until delivery. A tenth pregnant rat, by limiting its water supply to one containing a suspension of crystalline pregnenolone, ingested 655 mg. of the substance, with no ill effects. Using the same method, one of the castrate rats was given 675 mg. in eight days, which together with previous smaller doses, gave a total of 730 mg. in eighteen days. There were no gross or microscopic changes in the organs of any of these animals.

No other writer has reported undesirable clinical side effects after administration of pregnenolone. Hamblen has used up to 2,280 mg. in one fourteen-day period without ill effects. On 21 patients, Dr. Holloway and I have given up to 80 mg. daily, with a highest total dose of 1,140 mg. in fourteen days, with no complaints. One of us, 36 hours ago, took 250 mg. in a single dose, and so far has not been in any distress.

Our clinical results were variable and not always predictable. Unexplained dysmenorrhea was the most promising field, although even in the same patient, alleviation from month to month could not be assured. Unexplained uterine bleeding was not appreciably affected by pregnenolone. In a patient twenty-three years of age who had had only six menstrual periods in her lifetime, her first 2 consecutive periods followed 20 mg. a day of the synthetic preparation for fourteen days, but menses have not returned since pregnenolone was stopped.

All students of uterine physiology believe that one of the corpus luteum's effects is to decrease uterine irritability, and it has been conclusively shown in the rabbit and other animals that the uterus, under a full progesterone effect, does

given, and improved promptly when the dose was reduced. Of 2 patients who could not tolerate this drug, one had a known duodenal ulcer and the other a chronic cholecystitis. However, there were very few instances where the symptoms were severe enough to necessitate withdrawal of the drug. This finding of side effects is at complete variance with the results of all other observers, none of whom reported any disturbing symptoms. In order to determine whether kidney damage resulted from the oral administration of pregnenolone, urinalyses were made at the termination of the various series of treatment; no evidence of kidney damage was found.

TABLE V. UNDESIRABLE SIDE REACTIONS

	DAILY DOSAGE	
	15 MG.	30 MG.
Nausea	2	1
Nausea and vomiting	3	2
Abdominal pain and nausea	1	4
Weakness and dizziness		1
Severe headache		1
Total No. patients: 37	6	9—Total, 15 (31.0%)

It had been our original intention to use pregnenolone for the treatment of habitual and threatened abortion, but we hesitated to do so after noting the results of our animal toxicity experiments. The dosage of pregnenolone required to produce necrotizing changes in the kidney in rats is considerable for that animal; even the large and prolonged dose necessary for the treatment of habitual abortion may be well within the margin of safety in the human being. However, the question arose in our minds whether a steroid absorbed through the portal system should not be inactivated by the liver. Is pregnenolone orally active because it destroys the detoxifying function of the liver? Also, would impaired renal activity prevent or delay excretion of the drug, hence augment biologic effects? We would suggest that the patient be carefully watched for possible renal or liver damage should pregnenolone be used for the treatment of habitual or threatened abortion. Although we have obtained no clinical evidence of toxicity and urinalysis has failed to reveal any abnormality to date, no liver or kidney function tests had been performed in our clinical series.

The use of pregnenolone is contraindicated, in our opinion, in known cases of peptic ulcer, cholecystitis, hepatitis, and nephritis. The mild androgenic effects should not be construed as a contraindication, as Greene, Burrill and Ivy³ have shown that progesterone itself is androgenic in large doses.

CONCLUSIONS

Pregnenolone is a potent orally active progestational substance which produces both estrogenic and androgenic effects to a mild degree. It has been found definitely to cause suppression of the gonadotropic function of the anterior pituitary. Definite kidney damage was demon-

since we had our poorest results in this condition. One of our patients who was treated for menorrhagia without pain was given pregnenolone and subsequently complained of violent dysmenorrhea. Shortly thereafter, she was laparotomized and found to have polycystic ovaries. It is possible that her painless anovulatory bleeding was changed to painful menstruation by means of this progestin-like preparation.

We have not had the courage to use this drug in complications of pregnancy because of our animal experiments. Perhaps if Dr. Cornell continued the drug during the puerperium, he would also have suppressed lactation in his patient.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MAY 17, 1940

The following papers were presented:

An Evaluation of Androgenic Therapy in Gynecologic Practice. Dr. John W. Huffman. (For original article, see page 674.)

Laboratory and Clinical Experience With Oral Pregnenolone. Drs. Melvin R. Cohen, and Irving F. Stein. (For original article, see page 713.)

Presentation of a Specimen of Malignant Mixed Tumor of Uterus. Dr. Herman A. Strauss.

Ovarian Ectopic Pregnancy. Dr. Alfred F. Kobak.

The Rate of Entrance of Amniotic Fluid Into the Pulmonary Alveoli During Fetal Respiration. Dr. Franklin F. Snyder (by invitation).

not react to pituitrin or other oxytocic agents. Most workers believe that the human uterus, in situ, responds for all practical purposes similarly to that of the rabbit. Although uterine irritability is but one of a host of factors in the problem of abortion, it seems rather basic, and capable of study in the experimental animal. The following experiments were undertaken:

a. Immature female rabbits were primed over a period of six days with 50 gamma of estrone and then injected with 1 mg. daily of progesterone for five days. At this time, the histologic picture of the uterus was of a full progestational phase, and grossly the uteri were greatly enlarged and hyperemic. The results were as expected when strips of the uteri were suspended in an optimum bath. There was no response to from 0.01 to 10 units of pituitrin, although, as you can see in the tracings, the spontaneous uterine motility was not affected.

b. Similar rabbits were then "primed" or sensitized as before and no other treatment given for five days. Others were primed and then treated with estrone injections for five days. Both of these groups showed a marked uterine response to even 0.01 unit of pituitrin.

c. Then animals were given nothing but from 1 to 10 mg. daily of pregnenolone. After five days their uteri were in a partial progestational phase, and you can see the definite response to injections of even small amounts of pituitrin into the bath.

Those animals that were primed and then treated with oral pregnenolone 1 mg. daily for five days, showed a more developed progestational phase, and a more marked response to pituitrin, while those receiving 5 and 10 mg. daily for five days after priming displayed a complete progestational effect and the marked response to pituitrin. The increased uterine tone and magnitude of contractions is striking.

In conclusion then, we have a new synthetic preparation which can produce a progestational endometrium, is estrogenic and weakly androgenic, and increases uterine irritability. Its toxicity I have not been able to demonstrate. Its therapeutic indications are not clear in my mind, and in the face of its effect upon uterine irritability, I do not feel that at present it is indicated in the treatment of threatened abortion.

DR. EDWARD L. CORNELL.—A few months ago I was called to see a woman pregnant in her fifth month who in her two previous pregnancies had miscarried and was now having uterine contractions. I had just been informed about this drug, pregnenolone, and I thought it was a good opportunity to try it. I began with a 10 mg. dose and gave her 10 mg. every four hours for the first two days. The contractions stopped. Then she took it every six hours, and finally three times a day. At the end of ten days she was able to discontinue the drug and went along without difficulty for two or three months.

At the beginning of the eighth month she started to have labor pains and by the time I saw her she had produced a 4 cm. dilatation of her cervix. She had begun pregnenolone again, one tablet with the first contraction, and another in a couple of hours. When I saw her six hours later I gave her two tablets and sent her into the hospital. Then I gave her 19 mg. every two hours during the day and night. She was in the hospital for about ten days. The contractions had ceased, but the dilatation remained the same. Then the drug was given every six hours day and night.

She took a total of 4,400 mg. At term she was delivered of a baby weighing 5 pounds and 15 ounces. She has now gone home perfectly well and the baby is all right. There were no hyaline casts or albumin in the urine.

DR. COHEN (closing).—Dr. Burge's toxicity experiments were not exactly comparable with ours. He administered the drug orally in huge quantities over a short period of time while I used less of the drug over a longer period—about forty days, which might be regarded as equivalent to eighteen months in the human being. It is possible that a long period of administration of pregnenolone may affect the kidney whereas a large dose over a shorter period may have no effect.

I cannot account for the lack of nausea in patients treated by Dr. Burge. It is surprising to us that Dr. Burge reported his best results in cases of dysmenorrhea,

- New England Obstetrical and Gynecological Society.** *President*, Thomas Almy. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, Alice F. Maxwell. *President-Elect*, John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. Next meeting, San Francisco, Calif., Nov. 6 to 9, 1940.
- Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, H. C. McGee. *Secretary*, H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, Percy H. Swahlen. *Secretary*, Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Floyd Bell. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, H. Reid Robinson, Galveston, Texas. *Secretary-Treasurer*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Marlin, Texas, October, 1940.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Russell W. Allen. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** *President*, E. J. Litzenberg. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June, 1941, Colorado Springs, Colo.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, Frederick H. Falls, Chicago, Ill. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.
- Central Association of Obstetricians and Gynecologists.** *President*, Jennings C. Litzenberg, Minneapolis, Minn. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, M. P. Rucker, Richmond, Va. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Norman F. Miller, Ann Arbor, Mich. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June 2 to 6, 1941, Cleveland, Ohio.
- New York Obstetrical Society.** *President*, Thomas C. Peightal. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Roy W. Mohler. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, Frances Doyle. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, N. J. Eastman. *Secretary*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, April, and June.
- Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

The above cited examples had an immediate practical application to obstetrics and gynecology. However, there are many instances in which fundamental research work has been valuable not because of its immediate practical application but because of advancing knowledge or setting at rest controversial topics. Our researches here presented fall in this latter category.

The subject to be discussed can best be approached in the form of a question: Where is the site of formation of the powerful posterior pituitary hormones, present in extracts, such as pituitrin or pituitary liquid, which are so extensively and successfully used in clinical practice? It is a remarkable fact that here we have an extract which has been available for clinical use for a number of years, and yet some of the most fundamental questions connected with the active constituents of the extract have remained either unanswered or have been the subject of considerable controversy.

In attempting to isolate principles as chemical entities, it is desirable to know whether one or several active principles are being dealt with. This in turn raises the question as to the site of origin of these principles. We could not find an answer to either of these two questions. The literature was very confused. The leading authorities in the field, such as Harvey Cushing, Dean Lewis, and Sir Humphrey Rolleston,⁵ maintained vigorously that the neural lobe of the pituitary gland, being made up essentially of neuroglia tissue, did not have secretory capacity, and therefore the hormones had to be formed either from cells of the pars intermedia or from breakdown products of these cells. Close scrutiny of the evidence in support of this view made it apparent that further experimental work was needed to reach a decision. The ordinary laboratory animals were quite unsuitable for this research because in them the neural and intermediate lobes are so intimately connected that no clear-cut separation is possible. We, therefore, had recourse to a procedure which has been most productive in the solution of complex biologic questions and of which physiologists, pharmacologists, and anatomists have availed themselves; namely, the comparative approach.

We searched the literature for species in which the three lobes of the pituitary gland were either quite distinct or easily separable; or, failing this, in which the gland was rearranged in such a way that the neural lobe would not be admixed with either the intermediate or anterior lobe. We found a clue in a paper published by Wislocki on the pituitary gland of the porpoise.⁶ He showed that the gland of this species had no distinct pars intermedia, and that the neural lobe was completely separated from the anterior lobe by a thick fold of dura. Our first efforts to obtain porpoise pituitaries were unsuccessful, and therefore we turned our attention to the collection of pituitary glands from whales.

Through the cooperation of the Consolidated Whaling Company, we were permitted to visit their two stations on the Queen Charlotte Islands in British Columbia, where we obtained glands from the sperm, finback,

American Journal of Obstetrics and Gynecology

VOL. 40

NOVEMBER, 1940

No. 5

American Gynecological Society

Sixty-Fifth Annual Meeting, June 17, 18, and 19, 1940

THE COMPARATIVE ANATOMY AND PHARMACOLOGY OF THE PITUITARY GLAND OF UNUSUAL "EXPERIMENTAL" ANIMALS*

E. M. K. GEILING, M.D., CHICAGO, ILL.

(From the Department of Pharmacology of the University of Chicago)

CERTAIN of the recent advances in obstetrics and gynecology can justly be ascribed to the practical application of observations first made on laboratory animals by workers in the biologic sciences. One may refer to the researches being carried out at the Carnegie Institute of Embryology and at the Yale Laboratory of Primate Biology, where a number of investigators are making a cooperative study of the sexual cycle and the embryology of monkeys and apes. Because of certain similarities between these species and man, the information gained through these investigations contributes greatly to our understanding of the physiology of the gonads and of the development of the human embryo.¹

Another striking example of application of experimental data to clinical needs is the introduction of pituitary liquid into obstetrics and medicine.

Dale, in 1906,² in a paper dealing with the pharmacologic actions of ergot preparations on the uterus, mentions the fact that he observed a constrictor effect with posterior pituitary preparations. Three years later he published a more detailed report of this observation. However, in the meanwhile his preliminary announcement had suggested to Blair Bell the practical value of this observation, and after some further experimental studies Bell and Hofbauer became the first to use posterior pituitary in obstetrics.³

A third example is the observation by Aschheim and Zondek that the urine of pregnant women contains a gonadotropic substance. This discovery was used in the development of a test for pregnancy, and at present the Aschheim-Zondek test and the Friedman test are widely used diagnostic procedures.⁴

*Presented (by invitation) at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Que., June 17 to 19, 1940.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

lacking in birds, and from Mrs. Lewis of the Carnegie Institute of Embryology, we learned that a similar condition exists in the armadillo hypophysis. In consequence, pharmacologic and anatomic studies were carried out on the chicken hypophysis by DeLawder, Tarr and Geiling,¹¹ and on the armadillo hypophysis by Oldham.¹² The absence of a pars intermedia in both these species was confirmed, and the complete separation of anterior and neural lobes by collagenous connective tissue was established. Furthermore, assays of the separated lobes of both chicken and armadillo show that the melanophore-dispersing hormone is confined to the anterior lobe, and the oxytocic, pressor, and anti-diuretic hormones to the neural lobe. Essentially similar results were obtained by Oldham, McCleery, and Geiling in the hypophysis of a South American manatee.¹³

Assays of different areas of the anterior lobes of cetaceans and the armadillo indicate that the melanophore-dispersing hormone is present in higher concentration in the cephalic than in the caudal (juxtaneural) region.¹⁴ This is in agreement with the preliminary findings of DeLawder, Tarr and Geiling¹¹ in the chicken which were later confirmed by Kleinholz and Rahn.¹⁵ An investigation is now in progress to determine the first appearance of the hormone in the hypophysis of the developing chick embryo. We have already determined its presence in chicks of five days which is considerably in advance of any cellular differentiation in the anterior lobe.

Having been assured of the absence of the pars intermedia in the adult cetaceans, armadillo, and chicken, it was of importance to study the embryologic development of the glands in these species to determine whether a pars intermedia is present at any time during development. It will be recalled that in the human being, many authorities maintain that a discrete pars intermedia is lacking. However, studies of the developing human hypophysis such as those of Atwell¹⁶ and of Tilney¹⁷ prove conclusively that this portion is present during development and childhood, although it may become greatly reduced in the adult.

We were able to secure a representative series of armadillo embryos and the results of this study are now in press.¹⁸ In brief, it was found that the anterior and neural lobes are at all times completely separated by either a thick basement membrane or by vascular mesenchyme. Furthermore, while the caudal or juxtaneural wall retains its columnar epithelial appearance until development is fairly well advanced, in the later stages it becomes invaded by vascular connective tissue which breaks the cells up into the typical cell nests of the anterior hypophysis. Hence, at the time of birth, the lumen of Rathke's pouch has practically disappeared and the cephalic and caudal regions of the anterior lobe are essentially similar.

The collection of cetacean embryos is naturally a more difficult problem. However, we have been fortunate to secure a number of specimens, the pituitaries of which have been serially sectioned. In all, the anterior and neural lobes are completely separated by a thick septum of connective tissue. Only in the smallest embryos can the residual lumen be seen and in these the caudal or juxtaneural portion

blue, and humpback whales. Glands from the white whale were collected at Point Lebel on the St. Lawrence River, and during the summer of 1939 we were fortunate in securing glands from two species of porpoise, the speckled and the bottle-nosed, through the courtesy of the Marine Studios in St. Augustine, Florida. In all instances the glands were fixed for both histologic and pharmacologic purposes.*

The hypophyses of the various species of whales and porpoises are essentially similar⁷ and consist of a large flattened anterior lobe, a comparatively small neural lobe, and a well-developed pars tuberalis. There is no macroscopic or microscopic evidence of a pars intermedia. The anterior and neural lobes are completely separated by a thick dural septum and by the pia-arachnoid which encases the neural lobe.

The anterior lobe is composed of the characteristic nests of chromophobe and chromophil cells supported by a network of vascular connective tissue. The pars tuberalis is also well-vascularized and consists of small pale-staining cells and occasional colloid-filled vesicles. The neural lobe, for the most part, is made up of nerve fibers and pituicytes. The blood supply is rich and Herring bodies are scattered throughout the lobe. Nerve cells are present in the neural lobe of the porpoise but are not numerous.

It is apparent, therefore, that the anatomic relations of the cetacean hypophysis are such as to permit complete separation of the anterior and neural lobes, so that extracts may be prepared from either lobe without admixture of the other. For this purpose, the glands were removed as soon after the death of the animal as possible and the separated lobes placed in acetone to dehydrate and to defat them. They were then ground up into a fine powder and extracted with 0.25 per cent acetic acid, so that 1 c.c. of the extract contained the activity in 1 mg. of dried powder. The extracts were then assayed for their melanophore-dispersing, oxytocic, pressor, and antidiuretic activities by the standard techniques. All preparations were compared with the international standard powder.

The results of these experiments indicate that extracts of the neural lobe contain oxytocic, pressor, and antidiuretic activity but no melanophore-dispersing activity. Extracts of the anterior lobe, on the other hand, contain considerable melanophore-dispersing activity but only doubtful traces of pressor, antidiuretic, and oxytocic activity. Extracts of the pars tuberalis, which probably include portions of the neural stalk, contain varying amounts of all four activities.^{8, 9}

While the work on the cetacean hypophysis was in progress, search was made for other species which have no discrete pars intermedia. The description by de Beer¹⁰ and others indicated that this lobe is

*Acknowledgment is made of the generous financial aid which made possible the studies described in this lecture. This aid was furnished to us over a period of several years from various sources: Our search for suitable material was begun in 1934 under a grant from the National Research Council. During the years 1936 to 1938, we received substantial grants-in-aid from the Rockefeller Foundation. Since the summer of 1938 our investigations have been supported largely by a grant from the Committee on Research in Embryology of the National Research Council. By means of additional support from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago, we have been able to extend the scope of our research.

DOES THE NEUROHYPOPHYSIS HAVE AN ENDOCRINE FUNCTION?

Despite the very striking pharmacodynamic effects of extracts of the neurohypophysis, information concerning either its physiologic or pathologic role lacks finality. It may be of interest to compare the anterior and neural lobes of the hypophysis on the one hand with the cortical and medullary portions of the adrenal on the other, as appears in Table I.

TABLE I. COMPARISON OF PITUITARY AND ADRENAL GLANDS

Pituitary		Adrenal
Anterior lobe	Typical endocrine structure	Cortex
	Function and effects of extracts: Somatic and metabolic Complex interrelationship with other glands Number of hormones uncertain Effects of extracts slow in onset	
Intermediate lobe	Function in mammals unknown Regulator of melanophore cells in lower forms	-----
Neural lobe	Cells of nervous origin	Medulla
Neuroglia cells	Powerful hormones	Chromaffin tissue
	Pressor	
	Antidiuretic	
	Oxytocic	
	Effects of extracts prompt and of short duration	
	Action chiefly on smooth muscle structures	
	Role in animal economy still debatable	

Injection of neural lobe extracts causes striking changes in the cardiovascular, respiratory, and renal systems, the gastrointestinal tract, and the uterus. These effects are precipitous in onset and of short duration. While many of these changes are effected only by doses larger than could be considered physiologic, nevertheless they do furnish suggestive evidence of the possible functions of the neural hypophysis.

THE POSTERIOR PITUITARY AND WATER METABOLISM

Of the possible physiologic functions ascribable to the hormones of the neurohypophysis, the regulation of water metabolism seems best established from both the experimental and clinical approaches. Fisher, Ingram, and Ranson, and others^{19, 27} have shown that injuries resulting in the destruction of the supraopticohypophyseal tracts in laboratory animals result in diabetes insipidus which can be alleviated not only by injection of small amounts of the pressor fraction of the posterior pituitary but also by removal of the anterior lobe. These workers point out that the failure by a number of workers to produce diabetes insipidus may be due either to the fact that both lobes were removed or to incomplete destruction of the neural hypophysis, since it appears that functioning neural lobe tissue extends dorsally for some distance into the median eminence.²⁸ Clinical evidence of the

of the anterior lobe is similar in structure to the anterior region. Hence, we believe that in both the whale and the armadillo there is at no time during development a discrete pars intermedia comparable to that found in most other species.

DISCUSSION

Our studies on the site of elaboration of the oxytocic, pressor, and antidiuretic hormones receive ample support from the work of Fisher, Ranson, and Ingram.¹⁹ In an extensive series of experiments, these investigators produced diabetes insipidus in cats and monkeys by lesions in the region of the supraoptic nuclei. Examination of the pituitary glands of these animals reveals degeneration of the supra-opticohypophyseal tracts and atrophic changes in the pituicytes and loss of pressor, oxytocic, and antidiuretic activity. The anterior and intermediate lobes on the other hand are apparently unchanged, and there is no loss of melanophore-dispersing activity. Changes in the pituicytes have also been reported by Wang²⁰ and collaborators, following liberation of pressor, antidiuretic, and oxytocic activities by stimulation of the afferent vagus.

Gersh²¹ has recently described changes in the "parenchymatous" cells of the neural lobe (pituicytes) in response to a need for water conservation within the body, and he correlates these structural differences with changes in hormone content. While we have not applied Gersh's histologic methods to our material, nevertheless we did obtain some evidence that in the porpoise the hormone content is lowered in animals deprived of their food, which is the main source of metabolic water in cetaceans.²²

The possibility that the rich supply of nerve fibers in the neural lobe plays a role in the elaboration of the active principles has been advanced by Rasmussen,²³ but as Griffiths²⁴ has pointed out, the fact that the active principles may be recovered from tissue cultures of the neural lobe^{25, 26} does not support this contention, since in these experiments the nerve fibers have lost their connection with their cells of origin in the supraoptic nuclei. It is apparent, however, that more attention must be directed toward the histophysiology of the neural lobe before the final decision is reached as to the precise method of secretion of the active principles. This will undoubtedly necessitate the use of some other method than the capricious silver-staining techniques that most investigators have employed.

Since it is now accepted that all cells are capable of elaborating substances which may or may not play a physiologic role, there need no longer be any hesitancy in ascribing secretory function to cells of nervous origin. The work on the humoral transmission of nervous impulses indicates that powerful pharmacodynamic principles may be liberated at nerve endings. Furthermore, the cells of the adrenal medulla which are responsible for the formation of epinephrine have their origin in the neural crest. There seems, therefore, no reason to believe that the intrinsic elements of the neural lobe are incapable of giving rise to the oxytocic, pressor, and antidiuretic hormones.

Furthermore, one could conceive that while the pressor and oxytocic hormones have, in a sense, opposite actions, they may function in an harmonious way within the body to bring about the regulation as stated.

THE POSTERIOR HYPOPHYSIS AND PARTURITION

A question of special interest to gynecologists and obstetricians is whether the oxytocic principle of the posthypophysis plays a role in parturition. This subject has been reviewed recently by both Snyder³⁴ (1938) and by Reynolds³⁵ (1939). We agree with Snyder in his conclusion that the evidence on hand does not rule out the oxytocic hormone as a factor in normal parturition. The early failures to prevent parturition by removing the posterior lobe or severing the stalk must be reinterpreted in the light of more recent work which indicates that the characteristic structure of the neurohypophysis extends into the median eminence, hence all functioning posthypophyseal tissue was probably not removed by the early workers.

Of special significance is the recent report by Fisher, Magoun, and Ranson³⁶ that dystocia occurred in 7 cats in which diabetes insipidus had been induced by the destruction of the supraopticohypophyseal tract. Furthermore, Haterius and Ferguson³⁷ obtained contraction of the uterus by stimulation of the infundibular stalk. However, such contractions did not occur after electrolytic lesions were placed in the stalk.

Gersh²¹ reports a cellular hypertrophy in the neurohypophysis of the rat during or slightly after parturition which he believes to be correlated with hormone secretion; nevertheless, he points out that this may be attributable either to an increase in oxytocic hormone to assist in expulsion of the fetus or to an increased output of antidiuretic hormone to preserve the body fluid from excessive loss by the demands incidental to parturition (e.g., shedding of placenta, milk formation, and increased blood pressure).

According to Reynolds, the work of Fisher and his associates is open to the criticism that the anterior lobe was apparently also affected, since the animals did not subsequently go into estrus; while in regard to the work of Haterius and Ferguson, he suggests that the increased motility may be secondary to a transiently improved circulation.

That the sensitivity of the human uterus to posterior pituitary undergoes marked changes during both pregnancy and the menstrual cycle has been shown by Knaus,³⁸ Robson,³⁹ Adair and Haugen,⁴⁰ and others. It is generally agreed that in many species, including the human being, the sex hormones are an important factor in the alterations in sensitivity of the myometrium to pituitrin. The fact that the corpus luteum hormone inhibits the contractions, normally initiated by pituitrin, has been used to explain the refractiveness of the uterus during early pregnancy. Estrone, on the other hand, increases the sensitivity of the uterus to pituitrin, and hence it has been suggested that the increased amount of estrin in the circulating blood towards the end of pregnancy acts in conjunction with the oxytocic hormone in the initiation of labor. While this hypothesis is an attractive one, it is obvious that further evidence is required before the posterior pituitary can be ascribed with certainty as a physiologic role in parturition.

role of the neurohypophysis in diabetes insipidus is available in such reports as those of Berblinger,²⁹ Biggart,³⁰ and Baker and Craft,³¹ in which post-mortem examination revealed either total destruction of the pars nervosa or degenerative lesions in the supraopticohypophyseal tracts accompanied by atrophic changes in the pars nervosa.

A POSSIBLE METABOLIC ROLE OF THE POSTERIOR PITUITARY

We found that certain well-defined circulatory and respiratory changes are elicited by the intravenous injection in dogs or the intramuscular injection into human beings of moderate doses of posterior pituitary extract or of the pressor fraction, pitressin.^{32, 33}

In dogs the following series of events are noted: For a brief period (five to ten minutes) immediately following the administration of the drugs, the venous blood draining the limbs becomes arterial in color and shows a high oxygen content, a rapidly rising lactic acid concentration, and a concomitantly lowered carbon dioxide content. There is at the same time a precipitous decrease in total oxygen consumption and a lowering of the cardiac output. In the immediately ensuing recovery period, which persists for one and one-half to two hours after the injection, the physiologic picture is reversed. An abnormally dark venous blood is found, indicating increased oxygen utilization by the "starved" tissues; a further rise in lactic acid is followed by a gradual return to the pre-injection level; the carbon dioxide content returns slowly to a slightly subbasal value. Total oxygen consumption and cardiac output show parallel increases above their pre-injection values and then gradually return to the basal level. In normal human subjects essentially similar changes are produced by the intramuscular injection of the above named preparations.

The changes induced by the oxytocic fraction, pitocin, are not as clear-cut as those produced by pitressin. Nevertheless, in appropriate doses purified pitocin causes a definite increase in oxygen consumption. Thus pitressin and pitocin have, in a sense, antagonistic actions.

It is clear from these facts that the extracts of the posterior pituitary gland, when injected into the body, can act rapidly and efficiently in regulating the exchange of metabolites between blood and tissues. Assuming that the extracts used represent the hormone as it functions in the body, then after the injection of even small doses of the extracts there would result a concentration of the hormone in the blood greater than under normal conditions. Whether the physiologic changes induced by such concentrations can be regarded as an exaggerated hormonal effect, or would be produced by any substance acting either through the capillary constrictor effect or directly on the tissue cells remains uncertain. Until these points are settled one can do no more than propose the following hypothesis: If we postulate that the action of the extracts represents that of the posterior pituitary hormone as it exists in the body, and that the injection of such extracts, although it be a crude imitation under exaggerated conditions, simulates the normal action of the hormone, then the posterior lobe of the hypophysis functions in the body as one of the regulators of metabolism.

American manatee, is such as to render diffusion of the active principles from one lobe to the other highly improbable. Furthermore, Wislocki⁵³ and his associates, in studies on the vascular system of the hypophysis, have shown that the blood supply of the anterior and neural divisions is practically independent, hence it is highly improbable that the active substances could be transported from one lobe to the other via the blood stream. Thus the presence of oxytocic, pressor, and antidiuretic hormones in the neural lobe of the above species provides indisputable evidence that these substances are elaborated by the intrinsic elements of the neural lobe, and therefore the older viewpoint that they arise from the cells of the pars intermedia can be rightly abandoned.

In spite of the spectacular pharmacodynamic activity of posterior pituitary extracts, we are unable to ascribe any specific function in the animal economy to the active agents of these extracts. However, experimental and clinical studies on diabetes insipidus strongly suggest that the pressor hormone is actively concerned in the regulation of water balance. A more general function in metabolism is indicated by the marked changes in the blood chemistry observed after injection of extremely small quantities of posterior lobe preparation.

The clinical use of the oxytocic activity of posterior lobe extracts is justifiably the basis for a query as to whether this substance is concerned in the physiologic mechanisms of parturition. A satisfactory answer to this question can come only after further research. This is likewise true for the hypothesis that associates eclampsia and pre-eclampsia with the pressor hormone of the pituitary gland.

REFERENCES

- (1) *Hartman, C. G.*: Endocrinology 25: 670, 1939. (2) *Dale, H.*: J. Physiol. 34: 163, 1906. (3) *Bell, W. Blair*: Brit. M. J. 2: 1609, 1909. (4) *Aschheim, S.*: Glandular Physiology and Therapy, 1935, p. 241. (5) *Rolleston, Sir H. D.*: The Endocrine Organs in Health and Disease, Oxford University Press, London, 1936, Humphrey Milford, p. 67. (6) *Wislocki, G. B.*: Arch. Surg. 18: 1403, 1929. (7) *Wislocki, G. B., and Geiling, E. M. K.*: Anat. Rec. 66: 17, 1936. (8) *Geiling, E. M. K.*: Bull. Johns Hopkins Hosp. 57: 123, 1935. (9) *Valsö, J.*: Klin. Wehnschr. 13: 1819, 1934. (10) *de Beer, G. R.*: Biologic Monographs and Manuals, 6: Edinburgh, 1926, Oliver and Boyd. (11) *DeLawder, H. M., Tarr, L., and Geiling, E. M. K.*: J. Pharmacol. & Exper. Therap. 51: 142, 1934. (12) *Oldham, F. K.*: Anat. Rec. 72: 265, 1938. (13) *Oldham, F. K., McCleery, D. P., and Geiling, E. M. K.*: Anat. Rec. 71: 27, 1938. (14) *Oldham, F. K., Last, J. H., and Geiling, E. M. K.*: Proc. Soc. Exper. Biol. & Med. 43: 407, 1940. (15) *Kleinholz, L. H., and Rahn, H.*: Anat. Rec. 76: 157, 1940. (16) *Atwell, W. J.*: Am. J. Anat. 37: 157, 1926. (17) *Tilney, F.*: Bull. Neur. Inst., New York 5: 387, 1936. (18) *Oldham, F. K.*: Am. J. Anat. In press. (19) *Fisher, C., Ingram, W. R., and Ranson, S. W.*: Diabetes Insipidus and the Neuro-humeral Control of Water Balance, Ann Arbor, 1938, Edwards Brothers, Inc. (20) *Wang, Kun-jen*: Chinese J. Physiol. 13: 405, 1938. (21) *Gersh, I.*: Am. J. Anat. 64: 407, 1939. (22) *Geiling, E. M. K., Vos, B. J., and Oldham, F. K.*: Endocrinology 27: 309, 1940. (23) *Rasmussen, A. T.*: Endocrinology 23: 263, 1938. (24) *Griffiths, M.*: Proc. Linn. Soc. N. S. W. 63: 89, 1938. (25) *Geiling, E. M. K., and Lewis, M. R.*: Am. J. Physiol. 113: 534, 1935. (26) *Anderson, E., and Haymaker, W.*: Proc. Soc. Exper. Biol. & Med. 33: 313, 1935. (27) *Richter, Curt*: Proc. Assn. Res. on Nerv. & Ment. Dis. 17: 392, 1936. (28) *Weaver, T. A., and Bucy, P. C.*: Endocrinology 26: 920, 1940 (Advance abstract). (29) *Berblinger, W.*: Endokrinologie 20: 305, 1938. (30) *Biggart, J. H.*: Edinburgh M. J. 43: 417, 1936. (31) *Baker, A. B., and Craft, C. B.*: Endocrinology 26: 801, 1940. (32) *Grollman, A., and Geiling, E. M. K.*: J. Pharmacol. & Exper. Therap. 46: 447, 1932. (33) *Geiling,*

POSTERIOR PITUITARY AND ECLAMPSIA

The fact that the vascular and renal changes produced by injections of posterior lobe preparations into animals and man resemble so closely the signs and symptoms of eclampsia or pre-eclampsia prompted the suggestion that these baffling disease entities might be due to hyperfunction of the neurohypophysis. Numerous attempts have been made to demonstrate the presence of the pressor or oxytocic hormones in the blood of such patients. Positive findings were reported by Anselmino and Hoffmann⁴¹ (1931), but their results have not been confirmed by later workers such as Byrom and Wilson,⁴² and Melville.⁴³ The possibility remains that the tissues of the pre-eclamptic or eclamptic patients may be unusually sensitive to the posterior lobe hormones. This postulate receives support from the work of Dieckmann and Michel,⁴⁴ Lambillon and Schoekaert,⁴⁵ and of deValera and Kellar,⁴⁶ who found that eclamptic or pre-eclamptic patients responded to injections of pitressin with a rise in systolic blood pressure and a marked decrease in urine volume, whereas normal pregnant women were relatively insensitive. Dieckmann and Michel⁴⁴ believe that their results have a double implication: "(1) The injection of pituitrin per se may be dangerous in toxemic patients even in small amounts . . . (2) Pituitary extract in minute doses offers a good test in differentiating pre-eclampsia from vascular-renal disease in pregnancy."

From this brief discussion it is evident that additional research will be necessary before the neurohypophysis can be assigned an etiologic role in the toxemias of pregnancy.

MISCELLANEOUS EFFECTS OF POSTERIOR PITUITARY EXTRACTS

Extracts of the pressor hormone of the posterior pituitary usually stimulate the smooth muscle of the large intestine, and therefore such preparations have been used to restore intestinal tone postoperatively. In much larger doses, they lead to gastric erosion in the region of the hydrochloric acid secreting cells of the stomach (Dodds, Noble and Smith, 1934⁴⁷). This effect appears to be due to local ischemia resulting from vasoconstricting action of the pressor hormone. However, the high doses required to produce these lesions make it improbable that the neurohypophysis plays a role in the etiology of gastric ulcers.

Dodds⁴⁸ and his associates have shown that large doses of posterior pituitary extract lead to anemia which, they thought, was due to an increased blood destruction. Gilman and Goodman,⁴⁹ on the other hand, believe the anemia to be due to hemolysis of the cells arising from a dilution of the blood as a result of increased water retention. It is of interest to record that Noble, Binderknecht and Williams⁵⁰ have recovered material possessing pressor and antidiuretic activity from a patient suspected of having hyperfunction of the posterior pituitary. The symptoms of this patient were described by Jones⁵¹ and included hypertension, hyperchromic microcytic anemia, achlorhydria, and abnormal carbohydrate metabolism. For a more detailed account of the possible pathologic effects of hypersecretion of the posterior lobe reference should be made to the excellent summary by Liu.⁵²

SUMMARY OF CONCLUSIONS

The complete separation of the anterior and neural lobes of the hypophysis of cetaceans, the armadillo, the chicken, and the South

FUNCTIONAL AND GROWTH CHARACTERISTICS OF STRUMA OVARIII*

LUDWIG A. EMGE, M.D., SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

THE story of ovarian strumas is too well known to warrant repetition. The literature was recently reviewed in great detail by Nicholson and by Neumann. The purpose of this paper is to discuss certain functional qualities of these tumors and to evaluate their clinical significance.

GENERAL CONSIDERATIONS

The histogenesis of ovarian strumas is obscure. It is simplest to accept them as regional teratomas regardless of the fact that they may represent reduced one-sided developments as in so-called pure ovarian strumas, or may be part of a totipotent development involving all three germ-layers. It is possible that they constitute the adult phase of anlage displacements, although some claim that they are the result of some obscure unorganized ovogenic development. It is reasonably certain that they are *not* the result of thyroid metastases into an ovary, since this is contrary to the behavior of metastasizing thyroid neoplasms. It also is reasonably certain that they do not represent colloid degenerations of cysts arising from the many different forms of tubular structures with which the ovary swarms. Differential staining qualities of colloid and certain morphologic stigmata of the parenchyma leave little doubt that ovarian strumas are made up of aberrant thyroid tissue.

FUNCTIONAL CHARACTERISTICS

Since 1889, when Boettlin described thyroid in a dermoid, reports of some 150 cases of ovarian strumas have found their way into the medical literature, about 40 of which have been reported in this country.† The actual incidence is not known. Casual statistics based on individual experiences place it at from 2 to 15 per cent of ovarian teratomas, mainly dermoids. We found it to be 4 per cent in our material. Since the discovery of thyroid tissue in ovaries depends entirely upon a readily recognizable tissue mass or on good luck in making a microscopic search, small strumas may be easily overlooked. It has been pointed out repeatedly that extensive microscopic studies will reveal minute areas of thyroid tissue in many ovarian teratomas, just as minute rem-

*Read at the Sixty-fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Que., June 17 to 19, 1940.

†1904, Anspach; 1909, Frank, Wood, Norris; 1910, Proescher and Roddy; 1913, Outerbridge; 1914, Strong, Ries; 1925, Koucky; 1926, Rohdenburg, Simpson; 1928, Frankel and Lederer; 1929, Moench; 1930, Shapiro; 1931, Plaut; 1933, Masson and Mueller; 1934, Lyday; 1936, Cantor and Kogut; 1940, Wynn, McCarthy, and McClendon, Emge.

- E. M. K., and DeLawder, A. M.*: Bull. Johns Hopkins Hosp. 51: 1 and 335, 1932. (34) *Snyder, F. F.*: Physiol. Rev. 18: 578, 1938. (35) *Reynolds, S. R. M.*: The Physiology of the Uterus, 1939, Hoher. (36) *Fisher, C., Magoun, H. W., and Ranson, S. W.*: AM. J. OBST. & GYNEC. 36: 1, 1938. (37) *Haterius, H. O., and Ferguson, J. W. K.*: Am. J. Physiol. 124: 314, 1938. (38) *Knaus, Hermann*: Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes, Vienna, 1934, W. Maudrich. (39) *Robson, J. M.*: Recent Advances in Sex and Reproductive Physiology, Philadelphia, 1934, P. Blakiston's Son & Co. (40) *Adair, F. L., and Haugen, J. A.*: AM. J. OBST. & GYNEC. 37: 753, 1939. (41) *Anselmino, K. J., and Hoffmann, F.*: Arch. Gynäk. 147: 597, 1931. (42) *Byrom, F. B., and Wilson, C.*: Quart. J. Med., New Series 2: 361, 1934. (43) *Melville, K. I.*: J. Exper. Med. 65: 415, 1937. (44) *Dieckmann, W. J., and Michel, H. L.*: AM. J. OBST. & GYNEC. 38: 131, 1937. (45) *Lambillon, J., and Schockaert, J. A.*: Bruxelles-méd. 17: 1468, 1937. (46) *De Valera, E., and Kellar, R. J.*: J. Obst. & Gynaec. Brit. Emp. 45: 815, 1938. (47) *Dodds, E. C., Noble, R. L., and Smith, E. R.*: Lancet 2: 918, 1934. (48) *Dodds, E. C., and Noble, R. L.*: Nature 135: 788, 1935. (49) *Gilman, A., and Goodman, L.*: Nature 143: 379, 1939. (50) *Noble, R. L., Rinderknecht, H., and Williams, P. C.*: Lancet 1: 13, 1938. (51) *Jones, E. I.*: Lancet 1: 11, 1938. (52) *Lin, S. H.*: Chinese Med. J. 55: 448, 1939. (53) *Wislocki, G. B.*: Proc. Assn. Res. on Nerv. & Ment. Dis. 17: 48, 1938.

metabolism, and unless such a tumor is large it can be overlooked. A patient whose case illustrates this point came under our care in 1929.

CASE 1.—G. C., a doctor's wife, 31 years old, had been treated medically for mild Graves' disease for several years. She had borne two children, with no complications, and had not been examined pelvically for several years. Her basal metabolic rate had fluctuated between plus 34 and plus 12 per cent, with various bouts of severe tachycardia. Her medical attendant reported that rest and iodine therapy had benefited, but never relieved, her. Thyroidectomy had been considered but was postponed, fortunately, because of the patient's distaste for operations. Late one night an acute attack of severe right lower quadrant pain accompanied by vomiting led to the discovery of a twisted pedicle cyst of the right ovary, considered a dermoid because of its firmness. Operation yielded a tumor 10 by 6 by 6 cm. made up of various dermoid structures which included a large island of thyroid tissue in a state of early hyperplasia (Fig. 1). Judging from the morphology alone, one would not expect such a high degree of hyperthyroidism. However, this coincides with the experience of others. In this case, toxic symptoms abated within forty-eight hours and at the end of ten days the patient was completely free from toxic manifestations. On the fourteenth day her basal metabolic rate had dropped to minus 14 per cent. Neither chemical nor biologic assays were done, but the clinical evidence is so striking and the morphologic appearance of the tissue so suggestive that there can be little doubt the thyrotoxic state was caused by this struma ovarii.

Similar observations have been reported by Moench, Kovacs, Morgen, Kleine, Aschkanasy, Cantor and Kogut, and Neumann. In each instance, hyperthyroidism was corrected by removal of an ovarian struma. Kleine and Neumann report particularly striking cases with metabolic rates of plus 30 and plus 40 per cent which were somewhat improved by medical treatment but relieved only by removal of the tumor. In none of the cases reported was the morphologic change as striking as one would expect to find had the condition been produced in the thyroid gland.

We encountered a second case recently, still more interesting because of the unusual combination of thyrotoxicosis with metastatic ovarian strumosis.

CASE 2.—R. E. B., 20 years old, primipara, white, of Russian-American extraction, came to our clinic on March 19, 1938. She had married in December, 1937, menstruated last on Jan. 28, 1938, and separated from her husband in March. Finding herself pregnant, she went to an abortionist who discovered a pelvic tumor and refused to help her. She then consulted her own physician, Dr. E. D. Torre, who directed her to us.

Menarche occurred at the age of 17, but was followed immediately by twelve months of amenorrhea, so that regular menstruation was not established until the patient was eighteen years old. Since then, the menstrual cycle has varied from twenty-one to twenty-five days, lasting three to four days, with a normal amount of flow and without discomfort. General health had been fair and uneventful, until she noticed an increasing nervous irritability.

Pelvic examination revealed a pregnancy of about two months. The uterus was pushed backward and to the left by a large right ovarian tumor of limited mobility, rising to the level of the promontory of the sacrum. General examination of the patient revealed nothing unusual except a pulse rate of 100, interpreted as an expression of anxiety. Blood studies showed a mild anemia, with 4,000,000 red cells and 86 per cent Hg, a coagulation time of five minutes, and a bleeding time of two minutes. Blood pressure registered 98/50, and the net body weight was 125 pounds. Urine studies revealed no pathology. The basal metabolic rate was not

nants of other germ layers can be found in most so-called pure ovarian strumas if the search is carried far enough. In fact, Neumann recently voiced the opinion that probably there is no such thing as a pure struma ovarii. This, in itself, is of no great consequence, but what is more important is the fact that an ovarian struma (and not necessarily a very large one), under conditions yet unexplained, can seriously unbalance the metabolism of the body and at times invade other tissues through metastatic growth. According to existing reports, 8 strumas of the ovary have produced metastases, and a slightly larger number are described as having caused thyrotoxic symptoms. It is this group which attracts our attention, because we have encountered two instances of hyperthyroidism accompanying such tumors, one of which, in addition, produced extensive metastases.

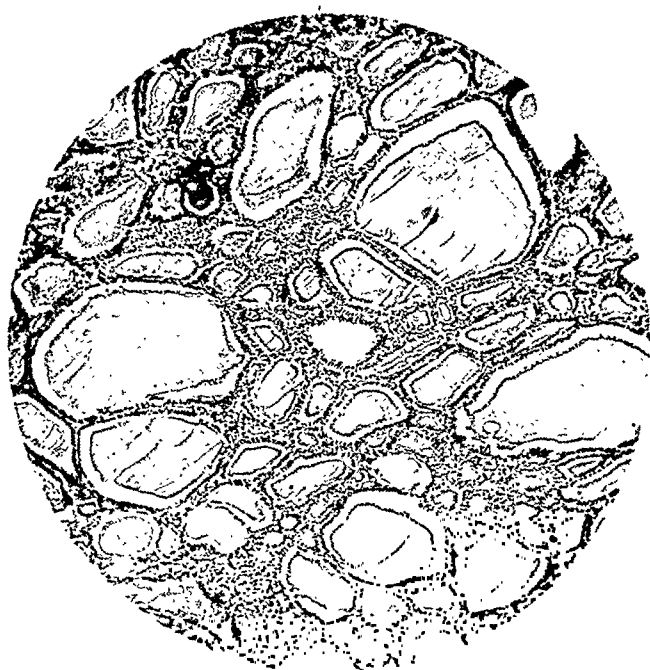


Fig. 1.

Most ovarian strumas are silent unless mechanical difficulties arise, and the greatest number, by far, are not diagnosed until they reach the laboratory. In fact, most of them are discovered accidentally, either because of size or because of pedicle-twists, or in the course of routine pelvic examinations. It is common, therefore, for them to come to operation without critical metabolic studies and, as a consequence, milder types of hyperthyroidism are undoubtedly overlooked.

Since these tumors consist of various quantities of thyroid tissue it is reasonable to presume that they function like the thyroid. Very little is known about this, partly because of their rarity and partly because they seem to reach a state of functional inactivity resembling, in certain respects, colloid goiters of the thyroid. Only occasionally is a tumor encountered which is active enough functionally to disturb

Langendorff cells, characterized by small dark nuclei and a very low cuboidal structure made up of deep-staining cytoplasm were present, but not abundant (Fig. 4). According to staining intensities, colloid at various stages filled most of the follicles. Hyperplastic areas were scarce and free from colloid. Where present, their follicles showed infolding with frequent mitotic activities. The supporting stroma

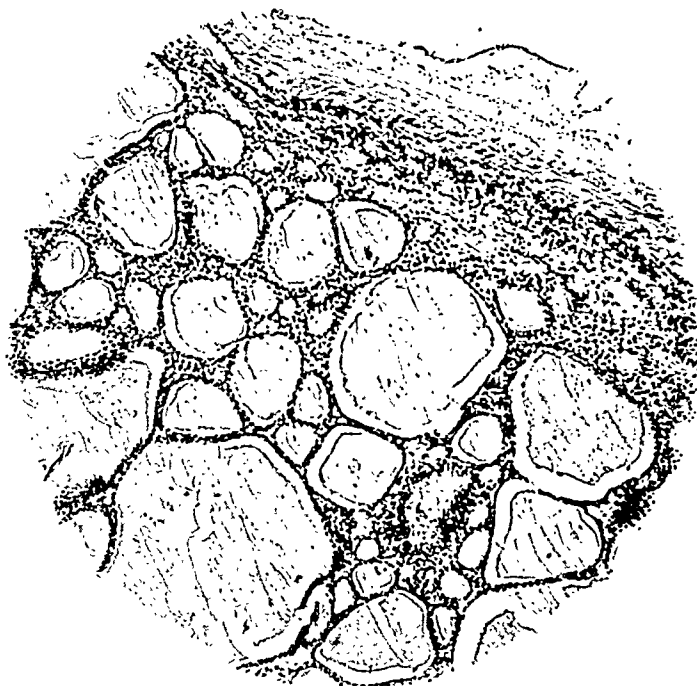


Fig. 3.

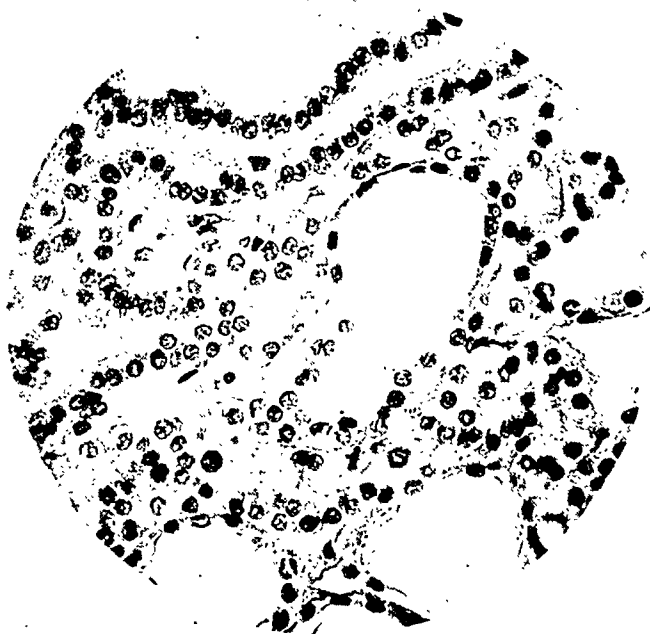


Fig. 4.

determined at this time. The preoperative diagnosis was pregnancy of two months' duration complicated by a large ovarian tumor, probably a dermoid. Struma was not suspected.

On March 31, 1938, the abdomen was opened and a large grayish tumor of the right ovary, having the appearance of a pseudomucinous cyst, was removed. Because of the presence of reddish growths in the omentum the tumor was assumed to be malignant and pregnancy was interrupted by hysterotomy. There was no free fluid in the abdomen. Recovery was uneventful. Microscopic study revealed both the neoplasm and the metastases to be composed exclusively of thyroid tissue in a state of colloid storage, and a diagnosis of pure struma ovarii with metastases was made.



Fig. 2.

Gross Description.—The tumor, grayish pink in color, measured 14 by 11 by 11 cm., weighed 400 Gm., and was irregularly globular. The cut surface showed a multilocular formation, individual components varying from a few millimeters to 2 or 3 cm. in diameter (Fig. 2). Some of the loculi contained a clear blood-colored fluid; others were filled with soft, pink or gray, spongy substances resembling colloid. A metastasis from the omentum 2 cm. in diameter had the appearance of fresh thyroid and showed fine follicles on the cut surface.

Microscopic Study.—All pieces taken from the large tumor showed a uniform resemblance to thyroid tissue, and no other type of organized tissue was found. The general architecture was that of follicle formation, each follicle being well defined and without a basement membrane (Fig. 3). Large groups of follicles were surrounded by dense layers of smooth muscle and connective tissue bundles. A number of these groups were enclosed in a more superficial areolar layer of connective tissue, probably of ovarian origin. Follicles were lined with single layers of low cuboidal cells with large vesicular nuclei. There were no ciliae and most of the cells were of the type described as "chief cells" of the thyroid. So-called

right ovary was well healed and free from recurrences. The outstanding observation was that all of the metastatic growths seemed to be superficially implanted. However, only those readily accessible were removed. Recovery was uneventful.

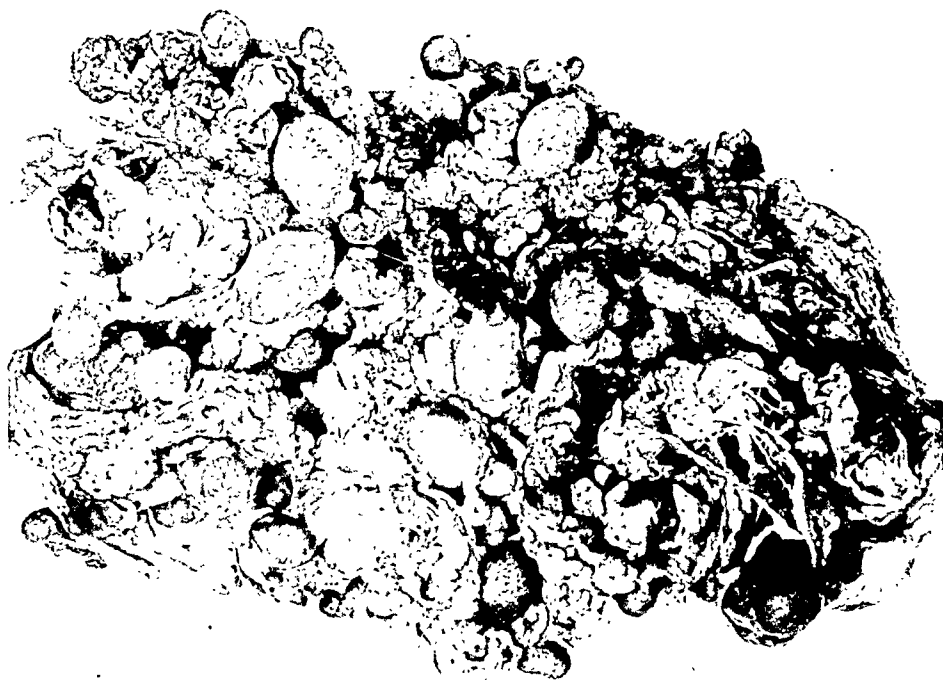


Fig. 6.



Fig. 7.

showed marked scarcity of connective tissue cells and contained free colloid. Long slender tubular follicles, probably produced by central pressure, were frequent toward the surface of the tumor (Fig. 5). Single mitotic figures were common throughout, usually located at a point where budding was taking place.

Implants from the perimetrium, the left ovary, and the omentum showed essentially the same structural architecture as the parent tumor, except that mitoses were not so evident.

On April 12, twelve days after operation, the basal metabolic rate was plus 6.3 per cent. On June 7 it had risen to plus 21.5. During the remainder of the year the patient became very nervous and lost ten pounds in weight, presenting a typical picture of Graves' disease. There was, however, no change in menstruation. The patient was then lost track of for a few months and when she reported in March, 1939, hyperthyroidism was still present but less pronounced. The basal metabolic rate was plus 16.5 per cent; there were no palpable abdominal masses and no discomfort or tenderness, and the blood picture had not changed. Because of the persistence of toxic symptoms, removal of omental metastases was recommended.



Fig. 5.

On March 22, 1939, all of the greater omentum (harboring many aberrant thyroids), with as much of the lesser omentum as was feasible, and some large nodules along the colic flexures, were removed. Altogether, there were probably between 50 and 60 smooth, firm, well-organized nodules which resembled normal thyroid tissue in color and texture. They varied from a few millimeters to 3 or 4 cm. in diameter. Each nodule was olive-shaped, and each was attached to the underlying structure by a thin pedicle carrying a well-developed vein and a small artery (Fig. 6). There was no sign of invasion of the adjacent structures, and no ascites. There were numerous other nodules along the lateral aspects of the ascending and descending colon, a few on the superior surface of the transverse colon, and a few along the parietal peritoneum over the bladder, the left ovarian ligament, and in the cul-de-sac. Deep-seated nodules could be felt in the mesentery of the sigmoid and small bowel. None of these was disturbed. The diaphragm, and the region of the kidneys, gall bladder, liver, and adrenals were free from metastatic growths. The left tube, left ovary and uterus appeared normal; the site of the

tumors still in an active state of growth have not been tested for iodine and hence no criterion is available. It is reasonable to assume that large colloid goiters of the ovary represent very low functional states and hence iodine storage may have dropped to insignificant levels. As matters stand, iodine levels of ovarian strumas not only vary considerably but do not parallel morphologic changes. Of the iodine determinations reported below, none fitted the morphology described on the basis of thyroid standards:

Neu, 1911		0.02% or 0.2 mg.	
King and Norris, 1930	I	0.11	1.1
	II	0.13	1.3
Plaut, 1931 to 1933	I	0.67	6.7
	II	0.02	0.2
Masson and Mueller, 1933	I	0.10	1.0
	III	0.13	1.3
	IV	0.01	0.1

Wynn, McCarthy and McClendon, using different standards, report 0.02 per cent for a colloid tumor and 0.009 per cent for its ischial metastasis with a reversed ratio for thyroid hormone iodine (0.005 per cent and 0.028 per cent). For the sake of comparison, their figures have been changed from micrograms to percentages. Our own experience with the results of two experienced investigators makes us doubt the constancy of iodine throughout a given tumor. This, together with technical differences, must seriously influence results. So far, iodine studies of ovarian strumas have not materially added to the knowledge of their functional activity. Such studies, however, have shown that ovarian strumas store iodine, though not in the same ratio to morphologic changes as does the thyroid gland. The functional importance of these tumors, on the basis of iodine determinations alone, cannot be great. However, clinical evidence permits the conclusion that in isolated instances ovarian strumas may produce thyrotoxicosis.

GROWTH CHARACTERISTICS

Most strumas of the ovary are benign tumors with orderly growth habits. It is not known when they begin nor how long they grow. They are decidedly more common after the age of maturity, and to my knowledge, are not encountered in early childhood. When part of an ordinary teratoma, they may not be encapsulated but may freely intermingle with other tissue. When they are encountered as a so-called pure struma they always have a capsule formed by mesoderm derivatives. Perforation of the capsule by direct invasion is extremely rare. Attempts to classify ovarian thyroids according to morphologic appearance into macrofollicular, microfollicular, and hyperplastic groups have been made by several investigators. There is, however, evidence that the morphologic structure of the ovarian tumor does not necessarily indicate its functional activity and hence no particular help is derived from such classifications. Besides, large tumors do not necessarily present a uniform morphologic picture but may show various stages of cellular activity in different regions of the tumor. In general, their tendency is to develop into a colloid goiter rather than to maintain hyperplastic activities, and it is granted that when the latter is present different degrees of hyperplastic action may occur within the same tumor. As a rule, the severer types of hyperplasia are rarely encountered.

Microscopic study of the omental implants revealed an entirely different picture. Hyperplastic changes with villous proliferation and infolding of the lining of follicles were more common, but mitotic figures were strikingly absent (Fig. 7). Mature follicles were distinctly larger, with a readily recognizable increase in Langendorff cells. In many follicles the cellular lining had become flattened to the point of compression of nuclei. The supporting stroma had increased considerably and extrafollicular colloid was hard to find. Hyperplastic areas, as before, were poor in colloid. The general picture was that of a well-organized thyroid struma with moderate hyperplasia.

On March 31, 1939, a bone survey was made and no metastases were found. On April 18 the basal metabolic rate had dropped to plus 4.0 per cent. By August, 1939, all symptoms of hyperthyroidism had disappeared, the basal metabolic rate now being plus 0.9 per cent, weight 122.5 pounds, pulse 72, blood pressure 107/88. The exophthalmus had markedly decreased. The abdomen was soft, and masses could not be palpated. A recent bone survey showed no visible metastases, and the basal metabolic rate has remained at plus 0.9 per cent.

Because of lack of facilities, iodine determinations were not made until after the tissues had been in Kaiserling's solution for from eight to twenty months. Since alcohol and formalin were used in the process of preparation, it is possible that certain protein-bound fractions of iodine were disturbed. However, as far as is known, total iodine contents are less affected and reasonably accurate information can still be obtained. Since different methods of determination may yield different results, tissue was sent to two different investigators.* Each received two metastases and one piece of the original tumor tissue. That sent to W. W. Hilty contained less colloid than that sent to A. L. Chaney. The total iodine levels expressed in milligrams per gram of tissue tested was as follows:

	HILTY		CHANAY	
Original tumor	1.055	0.982	0.085	
Metastatic tumors	1.650	0.743	0.086	0.021

Hilty's results correspond to those encountered in early hyperplasia of mildly colloid goiters. Those reported by Chaney would seem without significance were it not that he states in a personal communication that findings of 0.08 mg. per gram approached normal thyroid according to the method employed by him. The interpretation of iodine determinations therefore seems to depend upon standards established for a given method.

The total iodine content of the thyroid gland varies according to hyperplastic activities. According to Marine and Lenhart, morphologic changes parallel iodine content. Expressed in milligrams per gram of dried thyroid tested, they range as follows:

Normal state	2.17 mg. or 0.22%
Early hyperplasia	0.88 mg. 0.09%
Moderate hyperplasia	0.71 mg. 0.07%
Marked hyperplasia	0.32 mg. 0.03%
Colloid state	2.00 mg. 0.20%

It is pointed out that the thyroid gland may go through these various phases many times during the life of an individual without deviating from this ratio. It is not known that ovarian thyroid acts similarly. Most ovarian strumas are in an arrested state of colloid storage, frequently with no, or only traces of, demonstrable iodine. Smaller

*I am greatly indebted to W. W. Hilty, Control Chemist of Eli Lilly and Company and to A. L. Chaney, Chemist of the Los Angeles County General Hospital, for the determinations of iodine levels. Hilty and Wilson described their own method in *Industrial and Engineering Chemistry* 11: 637, 1939. Their method has been extensively used in the assay of defatted and dessicated thyroid. Chaney used a modification of the method of Matthews and Curtis, which digests the tissues without dessication in chromic and sulphuric acid.

fined to the abdominal viscera and are more often superficial than invasive. Omental metastases have been reported. Bone metastases, which is more in line with the behavior of malignant thyroid tumors, have been reported twice. In most instances, ascites has accompanied metastatic growth, although Wynn and others, as well as ourselves, found none. Metastases, if not invasive, seem to have a growth limit and may regress, as reported by Morgen. In the case reported here, the increase in size in omental metastases was comparatively small after one year, as far as could be determined at the second operation. At times, a parent tumor may appear morphologically benign and still produce malignant metastases. However, small areas of malignant degeneration may be easily overlooked.

The presence of metastases may or may not disturb the health of the host. The patient observed by us, though still harboring a large amount of aberrant tissue, continues in good health. Two bone surveys have failed to demonstrate metastatic invasion, which serves as a fair criterion for the relatively benign character of the growth. Patients may live many years with multiple aberrant thyroids, as demonstrated by Morgen's patient, who died at 74, eighteen and one-half years after operation, with known metastases still present at autopsy. Whether irradiation can arrest the growth of metastatic strumosis is conjectural. Werth described multiple metastases confined to the pelvis which were irradiated after removal of the genital organs. Unfortunately, the ultimate outcome of this case is not known. Metastatic growth, when it assumes malignant tendencies, usually kills quickly.

Table I sets forth some of the important observations described in conjunction with the 9 metastatic ovarian strumas now recorded.

The fact that some ovarian strumas can produce malignant metastases makes it imperative that careful study of the abdominal cavity be done at the time of operation and that bone surveys be made at least once a year thereafter. As described here, it is possible at times to remove safely part of the metastases, particularly when the condition gives rise to thyrotoxic disturbances, or when bone implantation has occurred, as described by Wynn and others. Ascites accompanies many of these tumors and, in itself, is not indicative of malignancy.

SUMMARY

1. It is estimated that from 5 to 6 per cent of ovarian strumas produce thyrotoxicosis.

2. Morphologic changes do not necessarily parallel the degree of toxicosis.

3. The majority of ovarian strumas store very little iodine.

4. The degree of iodine storage does not parallel morphologic changes.

5. From 5 to 6 per cent of these tumors produce metastases, half of which kill by malignant invasion.

6. Metastases are usually confined to the abdomen.

REFERENCES

- (1) *Anspach, B. M.*: Univ. Penna. Med. Bull. 16: 337, 1904. (2) *Aschkanasy, K.*: Monatschr. f. Geburtsh. u. Gynäk. 103: 203, 1936. (3) *Boettlin, R.*: Virchow's

Although there are no reliable figures, about 5 to 6 per cent of these tumors may be expected to assume metastatic growth habits. There are now nine such cases on record, including the one reported here (Table I). Metastases from an ovarian thyroid are not necessarily fatal. Only about one-half of the patients reported died as a result of metastatic invasion. Contrary to the behavior of metastatic neoplasms of the thyroid gland, metastases from an ovarian thyroid are ordinarily con-

TABLE I

AUTHOR	YEAR	DIED AFTER OPERATION	ASCITES	METASTASIS	REMARKS
K. Kretschmar	1904	21 mo.	+	Not stated	Many dense adhesions in abdomen. Died with ascites.
F. Proescher and J. A. Roddy	1910	2 yr.	+	+	Carcinomatous change of struma present at time of operation.
F. Proescher and J. A. Roddy	1910	1 yr.	+	+	Recurrence in 5 months in liver and mesentery. Mesenteric nodule same as parent tumor.
M. Morgen	1924	18½ yr.	++	+	Died from intercurrent disease at 74. Many small peritoneal implants at operation and at autopsy. (Benign strumosis.)
G. Werth	1928	Alive six months	+	+	Metastases restricted to pelvic organs. Radiated—discharged as cured. No further information.
P. F. Shapiro	1930	Autopsy diagnosis	+	+	Died from uremia. Strumosis considered benign; probably present for a long time. (Benign strumosis.)
L. D. Eesland	1936	Unknown	?	+	Original article not available. Metastases to cranium.
Wynn, McCarthy and McClendon	1940	Alive 3 yr.	0	+	Bone metastasis (ischium) 1 yr. postoperative—removed. Primary tumor had area of malignancy.
L. A. Emge	1940	Alive 2 yr.	0	+	Omental and mesenteric metastases. Hyperthyroidism. Second operation: No particular increase in size of metastases. Disappearance of toxic symptoms after removal of omental metastases. Probably benign strumosis.

to bed due to weakness and exhaustion on the slightest exertion, and the palpitation and dyspnea became gradually more marked.

In September, 1939, it was noticed that her abdomen was increasing in size, and she began to have frequency of urination. At this time, the pulse rate was 130 and emotionally she was much more unstable than prior to operation. The fine tremor of the fingers and the sweating of her palms became increasingly noticeable. In spite of these signs of persistent thyroid activity, the patient gained 25 pounds. For the first two months after leaving the hospital, she received Lugol's solution, minimis iii, but this was then discontinued.

On Nov. 15, 1939, the patient was re-admitted to the hospital. The most noteworthy change in the physical examination was increased abdominal enlargement and more extensive suprapubic dullness, this extending upward 7 cm. On gynecologic examination an indefinite, slightly tender mass was found in the right lower abdomen. Rectal examination revealed a large, round, smooth, slightly tender mass in the right adnexal region, the uterus being crowded into the left pelvis. A diagnosis of right ovarian cyst was made.

Basal metabolic rates were again determined and were found to be consistently plus 30. Routine laboratory work was normal. An iodine tolerance test was done which showed an extremely high fasting level, namely 48. The patient was treated as a case of hyperthyroidism but with no avail, the pulse remaining elevated.

As the patient continued to show signs of thyrotoxicosis after the subtotal thyroidectomy, it was felt that sufficient aberrant thyroid tissue might be present in the ovarian cyst and thus be the focus of the continued toxic symptoms. On Nov. 29, 1939, a laparotomy was performed by Dr. Edward P. Smith, and there was found a right dermoid cyst, small multiple myomas, and cystic degeneration of the left ovary. No evidence of malignancy or metastatic masses was observed. A bilateral salpingo-oophorectomy and a supravaginal hysterectomy were done. Immediately after operation, the pulse became quite rapid, reaching 130, but fell on the following day to 100. The convalescence was uneventful, the thyrotoxic symptoms quickly subsided, and the pulse rate soon dropped to 75. Eight days following the operation the basal metabolic rate was minus 6.

Pathologic Report.—"The right ovary measures 13.9 by 10.4 by 12.7 cm. A portion of the ovary is replaced by a cystic mass 3.5 cm. in diameter; the remaining portion is replaced by a solid tumor, 9 by 5 by 5 cm. On section, the cystic portion is found to contain hair and ceruminous material, while the wall is smooth-lined and moderate in thickness. This portion is typical of a dermoid cyst. The solid portion of the tumor on section is found to be divided up into lobules by trabeculae. The inner trabecular portions seem to be somewhat gelatinous in appearance, yet feel rather firm. Interspersed in the gelatinous portions are small areas of yellowish brown tissue. This solid area is suggestive of thyroid tissue. The myomatous uterus, tubes, and left ovary show nothing noteworthy."

Microscopic Description.—"In the sections of thyroid tissue from the ovary, there is marked variation in the size of the acini. Some are quite small, others are widely dilated. The lining cells vary from columnar to a flattened, scale-like type. Hyperplasia in areas is fairly well marked. Remnants of papillae and spurs are noted. Colloid is chromophile in character. There are a few lymphoid nodules present. Diagnosis: Hyperplastic goiter, involution stage."

Arch. 115: 493, 1889. (4) *Cantor, P. J., and Kogut, B.*: Am. J. Cancer 28: 760, 1936. (5) *Frank, R. T.*: Am. J. Obst. 60: 433, 1909. (6) *Frankel, J. M., and Lederer, M.*: AM. J. OBST. & GYNEC. 16: 367, 1928. (7) *King, E. S. J., and Norris, J. H.*: J. Coll. Surg. Australas. 3: 373, 1930-1. (8) *Kleine, H. O.*: Arch. f. Gynäk. 158: 62, 1934. (9) *Koucky, J. D.*: Ann. Surg. 81: 821, 1925. (10) *Kovacs, F.*: Arch. f. Gynäk. 122: 766, 1924. (11) *Lyday, R. O.*: Am. J. Surg. 25: 89, 1934. (12) *Marine, D., and Lenhart, C. H.*: Arch. Int. Med. 3: 66, 1909; 4: 440, 1909. (13) *Masson, J. C., and Mueller, S. C.*: Surg. Gynec. Obst. 56: 931, 1933. (14) *Moench, G. L.*: Ibid. 49: 150, 1929. (15) *Morgen, M.*: Virchow's Arch. 249: 217, 1924. (16) *Neu, M.*: Monatschr. f. Geburtsh. u. Gynäk. 34: 251, 1911. (17) *Neumann, H. O.*: Arch. f. Gynäk. 163: 600, 1937. (18) *Norris, C. C.*: Am. J. Obst. 60: 985, 1909. (19) *Nicholson, G. W.*: Guy's Hospital Reports 87: 391, 1937. (20) *Outerbridge, G. W.*: Am. J. Obst. 68: 1032, 1913. (21) *Plaut, A.*: Klin. Wchnschr. 10: 1803, 1931; AM. J. OBST. & GYNEC. 25: 351, 1933. (22) *Proescher, F., and Roddy, J. A.*: Am. J. Obst. 61: 619, 1910. (23) *Ries, E.*: Surg. Gynec. Obst. 18: 262, 1914. (24) *Rohdenburg, G. L.*: J. Lab. & Clin. Med. 12: 211, 1926. (25) *Shapiro, P. F.*: Ann. Surg. 92: 1031, 1930. (26) *Simpson, W. M.*: Surg. Gynec. Obst. 42: 489, 1926. (27) *Strong, L. W.*: Am. J. Obst. 70: 410, 1914. (28) *Werth, G.*: Zentralbl. f. Gynäk. 52: 2944, 1928. (29) *Wood, F. C.*: Proc. N. Y. Path. Soc., N. S. 9: 51, 1909. (30) *Wynn, H. M. N., McCarthy, J. S., and McClendon, J. F.*: AM. J. OBST. & GYNEC. 39: 263, 1940.

DISCUSSION

DR. JOHN MASON HUNDLEY, JR., BALTIMORE, MD.—During the past year a patient with struma ovarii, showing signs of thyrotoxicosis, has been observed in the Gynecological Department of the University of Maryland by Dr. Edward P. Smith, who has kindly given me permission to make this report.

H. H., 41 years of age, single, was admitted to the Mercy Hospital, May 9, 1939. She complained of a rapid pulse, heart irregularity, shortness of breath on exertion, and headaches, these symptoms having been present for the past five months. The past history was essentially negative. The menstrual history revealed nothing abnormal, the periods having always been regular, occurring every twenty-eight days, lasting two days, and being rather scant. During the past year, the patient has felt tired most of the time and has lost eight pounds.

She was a slender, nervous woman whose weight was 112 pounds. The eyes showed no signs suggestive of exophthalmic goiter, and the thyroid gland was not palpable. A slight pleuropericardial friction rub near the base of the sternum and a moderate degree of cardiac hypertrophy were present. The blood pressure was 139/72, pulse 110 with normal rhythm. An area of dullness was noted in the supra-pubic region, which extended upward nearly midway to the umbilicus. There was a fine tremor of the extended fingers. A pelvic examination did not seem indicated. The impression at this time was moderate cardiac hypertrophy with borderline decompensation. Hyperthyroidism, however, had to be ruled out.

The basal metabolic rate in six tests varied from a plus 22 to a plus 42. The electrocardiograms showed only a tachycardia. The teleoroentgenogram of the thorax showed nothing abnormal, no substernal thyroid being observed. Blood chemistry, blood counts, and serologic tests were normal, as were the examinations of the urine and stools. The sedimentation rate was 20 mm. in one hour.

A diagnosis of hyperthyroidism was then made, and the patient was placed on Lugol's solution, minims v, t.i.d., sedatives, and "thyroid" diet. The pulse improved with bed rest but the basal rate remained elevated. On June 2, twenty-three days after admission, a subtotal thyroidectomy was done by Dr. Daniel Pessagna, and the gland showed definite evidence of hyperplasia. The pathologic report is as follows: "In the sections from the thyroid, the acini were rather uniform in size. They were lined by cuboidal and flattened epithelial cells and contained chromophile colloid. A few small scattered areas of hyperplasia were noted. An occasional spur was seen. There were many nodules of lymphoid tissue scattered through the sections. The tissue was somewhat lobulated. *Diagnosis: Hyperplastic goiter, involution stage.*"

The patient had an uneventful convalescence and was discharged on June 15, 1939, but her progress at home was not encouraging. She was constantly confined

These figures show no well-defined connection between this type of ovarian carcinoma and menstrual abnormalities, certainly nothing of diagnostic significance. Any flow after the menopause should make one think of an endometrial metastasis or a primary tumor.

The operations done on these patients were as follows:

Hysterectomy, bilateral salpingo-oophorectomy	105
Hysterectomy, unilateral salpingo-oophorectomy	6
Bilateral salpingo-oophorectomy	7
Unilateral salpingo-oophorectomy	23
Exploratory	8
	<hr/> 149

We believe that the uterus and both tubes and ovaries should be removed whenever possible, because bilateral growths occur so often and metastases are found frequently in the back of the uterus. It is often difficult and possibly useless to attempt this, however, when the pelvis is filled with the growth and adherent omentum and intestine. The tumor should be removed intact, if possible, and tapping to decrease its size for easier removal should be reserved for elderly patients and poor risks.

We believe that when an operation for cancer of the ovary is done it would be wise to remove the omentum, regardless of whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrences later.

Sixteen patients had had previous treatment for pelvic disease. A patient of 47 years had had her uterus removed six years previously, for reasons unknown to us, and came in with generalized carcinoma, involving both ovaries. The ovarian tumors could have arisen since the operation. A 68-year-old patient had had some pelvic operation five years before, and we did an exploratory operation only because of the advanced disease. Another of 49 years of age had had one ovary removed five years before, and we found general metastases and removed the tumor of the other ovary. Another of 65 years had had an exploratory operation done at the age of 63. We could remove only one tumor because the disease involved the whole pelvis and abdomen. The same was true of another patient, aged 54 years, who had had an exploratory operation three years before. A 51-year-old woman had had an appendectomy six years previously, at which time a small cyst of the ovary was noted but not removed. We removed her uterus and both ovaries for a unilateral 8-inch cystic tumor, and she is well five and one-half years after operation. One patient, aged 37 years, had had a left oophorectomy nine years before, and we removed the uterus and right ovary for a 3-inch cystic tumor; she is still well five years after operation. There was probably no connection between the two.

A 45-year-old patient had had the menopause induced by x-ray at age of 35; she had had a left oophorectomy for a cyst said to have been malignant at age of 42, and we removed the uterus and right ovary for a 4-inch cystic tumor which ruptured during the operation. She had postoperative x-ray treatment and is well five years following operation. It would have been reasonable to have removed both ovaries and the uterus at 42, since she had already had the menopause.

A patient, aged 45 years, had had her left ovary removed eight years earlier and her uterus five years before we saw her. We excised the other ovary for an 8-inch cystic tumor, gave her x-ray treatment, and she is well 3½ years following operation. One patient, aged 42, had been operated upon for a cystic ovary four years previously, leaving a sinus. We were able to remove the uterus and other ovary, which were very adherent, gave her x-ray treatment, and she is apparently well two and one-half years after operation.

A woman, aged 55 years, had been treated with radium for flowing five years earlier, which induced the menopause. We found a unilateral semisolid tumor, re-

CARCINOMA OF THE OVARY*

FRANK A. PEMBERTON, M.D., BOSTON, MASS.

(From the Free Hospital for Women)

THIS paper is an analysis of 149 cases of primary carcinoma of the ovary occurring among a total of 855 patients with ovarian tumors, excluding retention cysts, treated in the Free Hospital for Women and its private ward by the various members of the staff from 1906 to 1938. It includes papillary, adenomatous, and medullary carcinomas. The classification and nomenclature of ovarian tumors are not standardized. We have decided to use Schiller's designation of adenopapillary carcinoma for these cystic types. They are subdivided into serous and pseudomucinous adenopapillary carcinoma, which appear to progress somewhat differently. Each of these is divided into those which show a gross semisolid structure of adenomatous tissue in part or whole and predominantly cystic ones. Finally, there are the medullary tumors.

MATERIAL

The age groups at which the tumor occurred are as follows:

20-30	4
30-40	17
40-50	46
50-60	47
60-70	28
70-	7
	<hr/> 149

The youngest was 26, but there are reports in the literature of still younger ones, Lynch having 1 of 16 years, for instance. The oldest was 86. The average age was 49. Sixty-one per cent occurred between the ages of 40 and 60. Therefore an ovarian tumor removed at any age must be considered as possibly carcinomatous.

Twenty-eight (19 per cent) were unmarried, which is near Lynch's 17 per cent and lower than in most reports. Eighty-one (66 per cent) of the 121 married women had from 1 to 10 living children, and 15 (12 per cent) had miscarriages only. Therefore, only 25 (22 per cent) were completely sterile. The first figure corresponds with Lynch's report that two-thirds of the married women had borne children, but 31 per cent of his patients had never been pregnant, as against our 22 per cent. It does, however, substantiate his argument that there may be an etiologic factor, in that women who develop cancer of the ovary show a reduced fertility.

The menstrual history of these patients is as follows:

Still menstruating:		
Normal	49	
Menorrhagia	7	
Metrorrhagia	7	
	<hr/>	
Menopause:		63
Natural	79	
Operative	4	
Radium	2	
X-ray	1	
	<hr/>	
		86
		149
Flow after menopause	6	

*Read at the Sixty-fifth Annual Meeting of the American Gynecological Society, Seigniory Clube, Que., June 17 to 19, 1940.

being adherent to other organs. The tumor was ruptured during removal in 34 (22 per cent) patients because it was adherent or necrotic in places. Metastases were general throughout the abdomen in 31 (20 per cent). They were described as confined to the pelvis in 25 (16 per cent), but in 16 of these the pelvis was practically solidly occupied by tumor masses. Adding these last two estimates, there were 36 per cent in which the extent of the disease should prevent a cure. Certainly earlier diagnosis is essential.

We have attempted to grade the degree of malignancy by considering the amount of differentiation and number of mitotic figures shown by microscopic examination. The tumors vary so much in their histologic appearance that it is difficult to grade them. The patterns and epithelial cells vary from a very simple papillary growth with low cells and not much invasion to semisolid adenomatous tumors with metaplasia, resembling carcinoma of the endometrium. Our result is as follows, Grade 1 being the least malignant:

Grade 1	49	32%
Grade 2	59	40%
Grade 3	41	28%

When graded in the subdivisions we obtain this result:

Grade	1	2	3
Serous adenopapillary carcinoma	36 (32%)	45 (39%)	33 (29%)
Pseudomucinous adenopapillary carcinoma	12 (43%)	12 (43%)	4 (16%)
Medullary carcinoma	0	1	5
Pseudomyxoma peritonei	1	0	0

This is further evidence that the serous are somewhat more malignant than the pseudomucinous tumors, since a larger proportion of them fall in Grades 2 and 3.

There were 6 medullary carcinomas, 2 of which were bilateral. They were all advanced, very adherent, and so friable that the tumors tore and were removed in pieces. In 2 cases an exploratory operation only could be done. One had a right salpingo-oophorectomy, 1 a bilateral salpingo-oophorectomy, and in 2 the uterus and both tubes and ovaries were removed. Five were graded at 3 and 1 at 2 for malignancy. There was 1 postoperative death and the others died in less than fifteen months. The longest survivor received 7,000 roentgens of x-ray after an exploratory operation. Another patient lived a year with the aid of a colostomy done for partial obstruction at the removal of her tubes and ovaries, the uterus having been removed three years previously elsewhere. These 6 patients were 41, 54, 57, 60, 64, and 78 years of age. Five were past the menopause, with no bleeding or discharge, and 1 was menstruating normally.

It would seem that these are very insidious tumors, in that they become adherent and grow without symptoms until it is too late for cure. The patients complained of discomfort in the lower abdomen only, except for 2 who had noticed some swelling.

The patient with pseudomyxoma peritonei was 34 years old in 1894 when she had a bilateral salpingo-oophorectomy for this bilateral tumor. At that time there were large masses of gelatinous material throughout the abdomen. In 1907, thirteen years later, she was again operated upon and the uterus and various masses of tissue were removed. The tumor was in all parts of the abdomen. She died two years later, fifteen years after the original operation. These are relatively benign but persistent tumors and may or may not be classed as true malignant ones.

moved the uterus and ovaries, gave her x-ray treatment, and she died in nine months. Another patient, aged 62, had had a cyst removed a year previous to our hysterectomy and unilateral oophorectomy for a 6-inch cyst which was very adherent, and she died of recurrence in one year. If she had had a radical operation the first time she might have been saved.

A 35-year-old patient had had an ovarian cyst removed eleven years before we did a hysterectomy and a right salpingo-oophorectomy for a cystic tumor. She is living nine years after operation with disease. One patient, aged 63, had had a hysterectomy and unilateral oophorectomy twenty-six years earlier, and we removed the other ovary for an adherent cystic tumor which ruptured, and she died in three years of heart disease, apparently cured of her cancer. Another patient, aged 69, had been treated with x-ray a year before, and we found bilateral cystic tumors. She appears to be well two and one-half years later. It does not seem to be generally realized that pelvic tumors arising after the menopause are nearly always ovarian and not fibroids of the uterus. So far as we could determine, this woman had been treated with x-ray on a diagnosis of fibroid. Finally, a patient, aged 49 years, was treated in our hospital with 1,200 mg. hr. of radium for menorrhagia two years before a tumor in the pelvis was felt. It was doubtless present at the previous examination but too small to be found. She not only had a semisolid ovarian tumor 5 inches in diameter, but early carcinoma of the endometrium and advanced carcinoma of the cecum, all different tumors. The endometrium at the radium treatment showed hyperplasia, but it is, of course, possible that there were areas of carcinoma which were not sectioned. She had no flowing after the radium treatment. We did a hysterectomy, bilateral salpingo-oophorectomy, and excision of the ascending colon. She received postoperative x-ray treatment and lived three years, dying of metastases in the upper abdomen and chest wall on the right, probably from the intestinal cancer.

The number of cases in the various pathologic divisions of these tumors are as follows:

Serous adenopapillary carcinoma, semisolid	44
Serous adenopapillary carcinoma, cystic	70
Pseudomucinous adenopapillary carcinoma, semisolid	10
Pseudomucinous adenopapillary carcinoma, cystic	18
Medullary carcinoma	6
Pseudomyxoma peritonei	1

The differentiation between serous and pseudomucinous is usually definite, but a few cases contained both, so the predominating type was chosen in such instances. The designation semisolid contains a large personal equation, and we have put in that class the tumors that had gross areas of semisolid tissue which showed an adenomatous appearance microscopically. The medullary carcinomas are solid tumors. In previous years many had been called solid carcinomas which, in light of more recent knowledge, proved to be granulosa cell tumors and were excluded from this series after I reviewed the slides. There is a difference of opinion as to whether or not pseudomyxoma peritonei is a malignant disease, but since it is progressive we have included our 1 case.

At operation the tumors were designated as unilateral or bilateral in all but 3 instances where the disease was so advanced that it could not be determined. The tabulation is as follows:

	UNILATERAL	BILATERAL
Serous	63 (53%)	55 (47%)
Pseudomucinous	25 (82%)	3 (18%)

Seventy-one cases (47 per cent) had enough ascites for it to be noted in the operative record. In 121 instances (80 per cent), the tumors were described as

Metastases from the ovary to the endometrium may occur by extension through lymphatics and veins, by direct growth through the uterine wall and by extension through the tube or implantation of free pieces of tissue flowing through the tube into the uterine cavity.

Sampson has described 12 instances of metastases in the lumen of the tube, 2 of our 6 cases under discussion show the same, and it is reasonable to suppose that the endometrial growth may have arisen from them. The ages of our 6 patients were 33, 36, 40, 43, 43, and 45 years. Cancer of the endometrium is uncommon under 45. This is another point in favor of the ovary-to-endometrium course in 5 of the above instances. Furthermore, in 4 of our cases the endometrial growth was small and at the top of the uterine cavity. Since such metastases occur, this is an added reason for doing a hysterectomy if possible. Forty-four (29 per cent) patients had other tumors. Fibromyomas of the uterus were present in 30.

Endometriosis was associated with the carcinoma in 10 instances. It is reasonable to suppose that this disease may be the source of carcinoma of the ovary, but it is difficult to prove the relation in any specific case, and we were not able to in these.

Benign serous cystadenomas occurred in the other ovary in 2 patients, a benign pseudomucinous cyst in 1, a cystadenofibroma in 1, and sarcoma in 1.

Carcinoma of the cecum was present as a primary tumor in 2 cases and carcinoma of the endometrium in 5.

Therefore, one should survey the field for other tumors before deciding on the method of procedure, and a curettage should be done as a first step; for with these 5 primary tumors of the endometrium and the 6 metastatic ones, there are 11 cases with involvement there.

There were 37 patients with semisolid serous adenopapillary carcinoma operated upon five or more years ago, and only one is living and well.

Untraced	4
Postoperative death	2
Dead	
0-1 year	12
1-2 years	10
2-3 years	4
3-4 years	2
8 years	1
28 years	1
Living 6½ years	1

Twenty-two (71 per cent) out of 31 that survived operation died before the end of the second year after operation. The patient that lived 8 years had a hysterectomy and bilateral salpingo-oophorectomy for a unilateral Grade 2 tumor and died of heart disease. The patient that lived twenty-eight years had a left salpingo-oophorectomy for a unilateral Grade 1 growth at the age of 47, and a year later the other ovary was removed for a serous cystadenoma. She died twenty-seven years later of heart disease; an autopsy showed no sign of cancer. The patient who was living and well after six and one-half years had a hysterectomy and bilateral salpingo-oophorectomy for a unilateral Grade 2 tumor and received 6,400 roentgens of x-ray after operation. This is certainly a discouraging list of cases, since only 3 out of 37 were apparently cured by treatment.

The picture is more cheering when we consider the cystic adenopapillary carcinomas, of which 53 were treated five or more years ago. The statistics are as follows:

Untraced	6		
Postoperative death	2	LIVING, WELL	
DEAD		5-6 years	7
0-1 year	10	7-8 years	1
1-2 years	5	8-9 years	2
2-3 years	3	13-20 years	6

There were 6 cases in which metastases occurred to the endometrium.

Patient 18-127, aged 33, white, married twelve years, entered the hospital May 23, 1911. She had had two children and one miscarriage. Her last pregnancy was eight years ago. Catamenia was normal, every twenty-eight days, lasting five days. Operation: Right salpingo-oophorectomy. Supravaginal hysterectomy. Cyst ruptured during removal. Pathology: Unilateral, adenopapillary carcinoma, right ovary, 12 inches in diameter. Adenocarcinoma, endometrium metastatic. The whole endometrium was involved. Tube negative. Untraced.

Patient 31-197, aged 36 years, white, married twelve years, entered the hospital May 1, 1919. There had been no pregnancies. Catamenia was menorrhagic for one year. Operation: bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, left ovary, 6 inches in diameter. Normal right ovary. Adenocarcinoma, endometrium metastatic, small area at fundus. Tubes normal. Well, twenty years.

Patient 27-51, aged 40 years, white, married fourteen years, entered the hospital Nov. 23, 1916. She had had six children. Her last pregnancy occurred four years ago. Catamenia was regular every twenty-eight days, lasting ten days, except for a period of six months when she had menorrhagia. Operation: Bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, right ovary, 5 inches in diameter. Normal left ovary. Adenocarcinoma, endometrium metastatic, small area in fundus. Tubes normal. Well, seven years.

Patient 2243, aged 43 years, white, married six years, entered the hospital May 17, 1928. There had been no pregnancies. The catamenia was normal and regular every twenty-eight days, lasting seven days. Operation: Bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, left ovary, 6 inches in diameter. Metastasis to right ovary. Endometrioma, right ovary. Adenocarcinoma, endometrium metastatic, small area in fundus. Metastatic carcinoma in lumens of both tubes. Died eight months after operation.

Patient 15-296, aged 45 years, white, married fifteen years, entered the hospital March 25, 1909. She had had one miscarriage fifteen years ago. Catamenia had ceased six months before entrance into hospital. There was no discharge. Operation: Bilateral salpingo-oophorectomy. Complete hysterectomy. Cyst adherent, ruptured during removal. Pathology: Adenopapillary carcinoma, right ovary, 10 inches in diameter. Normal left ovary. Adenocarcinoma of endometrium, metastatic, whole surface involved. Metastases in right tube and cervix. Untraced.

Patient 23029, aged 43 years, white, married fourteen years, entered the hospital on Jan. 15, 1933. She had had one miscarriage. Catamenia was normal and regular every twenty-eight days, lasting three days. Operation: Supravaginal hysterectomy. Bilateral salpingo-oophorectomy. Appendectomy. Pathology: Bilateral adenopapillary carcinoma of ovaries. Adenocarcinoma of endometrium, area 1.5 cm. in diameter, on left wall. X-ray treatment, 4,800 r. postoperative. Died five years after operation for metastasis in lung.

That metastases to the endometrium occur is recognized by various pathologists, but it is also acknowledged that it is often difficult to prove whether the tumor was primary in the ovary or uterus. Sternberg, in his section on ovarian tumors in Halban and Seitz, quotes Pfannenstiel, Arzt, Lessing and Schanta as believing that ovarian tumors may metastasize to the endometrium and Pfannenstiel says it is more common than the reverse. Boyd also agrees that it may occur. According to our figures, 6 ovarian tumors out of 149 metastasized to the endometrium, that is 4 per cent, while 12 out of 305 of endometrial cancers showed metastases in the ovary, that is 4 per cent.

Of those enumerated as dying more than five years after treatment, 3 died of cancer, 1 was apparently well at six years and then was lost trace of, and 1 died of pernicious anemia at fifteen years. The 7 living are apparently well. There was a five-year salvage of 12 (50 per cent).

These tumors may also be divided into 10 semisolid and 18 cystic for the total number of 28. Of the 12 patients surviving after five years, only 1 had a semisolid tumor; that is, the cystic ones are much less malignant.

To summarize, 114 of these patients with adenopapillary carcinoma were treated more than five years ago and 37 lived five or more years after treatment (32 per cent). The semisolid tumors of both types are much more malignant than the cystic ones and the serous type more so than the pseudomucinous.

The deaths for the 149 cases occurred at the following years:

Postoperative	10
0-1 year	33
1-2 years	26
2-3 years	9
3-4 years	6
4-5 years	5
5-6 years	2
6-7 years	2
8-9 years	2
12-13 years	1
14-15 years	1
15-16 years	2
28 years	1

Sixty-nine (47 per cent) did not survive more than two years.

The five-year end results of treatment as a whole are certainly discouraging. Some patients appear to be well on examination but may have areas which cannot be felt but will develop later, so a ten-year period of observation is necessary, as Lynch suggested. The percentage of five-year salvage varies in different reports from 10 per cent to 35 per cent. Our 32 per cent corresponds very nearly to Lynch's 35 per cent of all the tumors, and our 50 per cent salvage in the pseudomucinous type to Meigs' 50 per cent with the same. The striking fact in our series is that 36 per cent were obviously incurable when seen and Meyer says 55 per cent of his were.

Therefore earlier diagnosis is essential and that can be obtained only by preventive examinations, since these are silent growths for a long time. I have found only one ovarian tumor by that means in my private practice, but it is probable that few gynecologists have a large enough number of patients coming for yearly or semi-yearly examinations to discover many developing tumors of this type. This particular patient of 60 years had a benign serous cystadenoma grow, after a negative examination, to a size of 6 inches in the course of one year without symptoms of any kind. If other similar reports could be obtained the rate of growth could be determined.

Twenty-nine patients have received postoperative x-ray treatment. Sixteen are apparently well from two to six years after treatment, the average being 4.5. One is alive with disease four years from the first

3-4 years	2	LIVING, WITH DISEASE	
4-5 years	3	5 years	1
8 years	1	9 years	1
12 years	1	15 years	1
14 years	1		

Fifteen (28 per cent) out of the 51 that survived operation died before the end of the second year. Of those dead, the eight-year survivor died of cancer. The original operation showed a primary adenocarcinoma of the endometrium as well as the unilateral ovarian tumor in a woman 45 years of age. A complete hysterectomy and bilateral salpingo-oophorectomy were done. Recurrences were excised from the abdominal wall three and four years after the first operation but the disease continued. The twelve-year survivor died of diabetes and the 14-year one of heart disease; both apparently were cured of their cancer. There are 16 living and apparently well. Thirteen had a hysterectomy and bilateral salpingo-oophorectomy done. Two had a hysterectomy and right salpingo-oophorectomy done, the other ovary having been removed three and nine years before. We could not obtain the diagnosis on the first operations. The last patient is living and well thirteen years after a left salpingo-oophorectomy done at the age of 71 years. The tumor which ruptured during the operation was 10 inches in diameter, and the other ovary, which was left in, has apparently caused no trouble. Eight had bilateral tumors and 8 unilateral. The tumor was ruptured in 4 instances during removal. An eight-year survivor had definite peritoneal metastases, another had metastases in the omentum, which was removed, and a five-and-one-half-year apparently well patient had an everted papillary growth. These patients had tumors of low malignancy, 12 being Grade 1 and 4 Grade 2. Five of them were treated with x-ray after operation.

There are three living with the disease five, nine, and fifteen years after operation. The first had her uterus, tubes, and ovaries removed for a unilateral tumor which ruptured during the operation. She was treated with x-ray but received only 2,800 roentgens. The second patient had had her left ovary removed eleven years before for a malignant papillary cystadenoma. We did a hysterectomy and right salpingo-oophorectomy for a Grade 1 cyst, 8 inches in diameter, very adherent, and removed a metastasis in the abdominal wall. She has a mass in her pelvis which is being treated with x-ray. The last one, now at 15 years, had her uterus, tubes, and ovaries removed for bilateral tumors, 4 and 2 inches in diameter, which were adherent. They show a Grade 1 malignancy. She seemed well until six years ago, after which we lost trace of her, but last year she was tapped for ascites at the Brigham Hospital, and 10 quarts of fluid were removed. She received x-ray treatment. Cells removed from the fluid were consistent with carcinoma of the ovary.

Therefore in this series of 53 adenopapillary carcinomas, there are 16 patients alive and well more than five years after operation, 2 who died twelve and fourteen years after treatment, apparently cured of their ovarian tumors, and 3 surviving with disease, a five-year salvage of 39 per cent.

The total number of patients with serous adenopapillary carcinomas treated more than five years ago is 90, and there is a five-year salvage of 25, only 27 per cent.

There were 24 patients with pseudomucinous adenopapillary carcinoma treated more than five years ago.

Untraced	1		
DEAD		LIVING, WELL	
0-1 year	5	5-6 years	1
1-2 years	2	6-7 years	2
2-3 years	1	7-8 years	1
3-4 years	1	13 years	1
4-5 years	2	14 years	1
5-6 years	2	16 years	1
6-7 years	2		
15 years	1		

throughout the abdomen. Twenty-seven of our patients had general abdominal metastases and only 4 survived for more than two years. They died at three and three-fourths, four, four and one-half, and eight and one-half years, respectively. Most of the rest died within a few months, only 3 living more than a year. One cannot advocate no treatment, however, because such patients have nothing to lose and operation may prolong life in a few.

SUMMARY

Cancer of the ovary should be treated by as radical an operation as circumstances permit and that should be followed by x-ray treatment.

Preoperative x-ray treatment may make some apparently inoperable cases operable.

The omentum should be removed as a routine.

The solid and semisolid tumors are much more malignant than the mostly cystic ones.

The gross extent of the disease determines the prognosis but, other factors being equal, those of low malignancy survive longer.

The results of treatment are poor because the tumor grows silently until it is incurable in from 36 to 50 per cent of the cases.

Earlier diagnosis is essential and can be made only by preventive examinations.

REFERENCES

Lynch: AM. J. OBST. & GYNEC. 32: 753, 1936. *Halban and Seitz*: Biology and Pathology of the Female 5: 675, 1926. *Meigs*: South. M. J. 30: 133, 1937. *Baer*: Arch. Path. 26: 240, 1938. *Sampson*: Am. J. Path. 14: 385, 1938. *Boyd*: General Pathology, 1938.

DISCUSSION

DR. JOSEPH L. BAER, Chicago, Ill.—There are two points in Dr. Pemberton's paper, which I should like to emphasize. First, I find grading largely futile. For example, there was a type of carcinoma of the ovary which formerly was known as the small cell carcinoma of the ovary and which, under the microscope, has the appearance of utmost malignancy. Nevertheless, it is a relatively benign growth in the ovary which, in today's nomenclature, is known as a dysgerminoma. On the other hand, I reported in the anniversary number of the *Archives of Pathology*, dedicated to Dr. Ludwig Hectoen, an instance of a patient who had upon operation a literally inoperable abdominal condition, with bilateral solid ovarian tumors, with metastatic nodules all over the peritoneum and viscera, and extensive omental involvement. The condition was quite inoperable, but biopsy revealed a completely benign picture. This patient was subjected to vigorous roentgen treatment and after a number of months was operated upon again. It was found that there had been a complete disappearance of all the metastatic nodules, including nodules in the liver. The genital field was entirely operable. After operation the patient was subjected to further irradiation and is now entirely well. Experience with such cases makes me feel that microscopic grading has very little value so far as the prognosis or type of treatment is concerned.

Dr. Pemberton spoke of the routine resection of the omentum, which he considers to be useful for the prolongation of life and possibly to produce a cure. The omentum physiologically serves to cover the abdominal viscera but is not a shelter for the pelvic peritoneum, consequently metastases from the ovaries can readily reach the pelvic peritoneum. In the absence of the sheltering omentum overlying the abdominal contents, these metastases will be prone to invade the viscera directly. That may be of little consequence except for the fact that in our experience, which

treatment. Twelve had died at from one-half to six years; an average of two years.

The treatment was started usually about three weeks after operation and from 3,200 to 9,100 roentgens were given. We do not treat patients who are emaciated and in very poor general condition, because the gastrointestinal upset and toxemia following the application of x-ray may tip the scales adversely.

Twenty tumors were unilateral and 9 bilateral. They were graded as follows: 14 at Grade 1, 8 at Grade 2, and 7 at Grade 3.

There were evident pelvic metastases in 10, 4 of whom died in five months, ten months, two years, and two and one-fourth years, respectively. Three were Grade 3 and 1 Grade 2. There are 6 apparently well, 1 at two and one-half, 1 at three, 2 at four, 1 at five, and 1 at six years. Five of these were Grade 1 and 1 Grade 2. It would seem that the x-ray had been of benefit in these patients.

Three patients had general abdominal metastases and 2 were Grade 2, and 1 Grade 3. They died at eight months, eighteen months, and forty-five months, respectively. Their lives were perhaps prolonged to some extent.

There were no apparent metastases in 10 patients, 7 of whom are living: 1 at three and one-half, 4 at five and one-half, and 2 at six years. Five were Grade 1 and 2 Grade 2. The other 3 died as follows: 1 at one and one-half years from a metastasis in the brain, 1 at two years with a mediastinal metastasis, and 1 at six years with a lung metastasis, all Grade 1.

Six patients had no evident metastases but the tumor was ruptured during removal. Four of them are well at four, four, five, and five years, respectively, all Grade 1. Another patient with Grade 1 is alive with disease at four years and a patient with a Grade 2 died in nine months.

Sixteen (55 per cent) are apparently well, 1 is alive with disease, and 12 are dead. The series is too small and the time too short to draw accurate conclusions. Fifty per cent were Grade 1 as against 32 per cent for the whole series of 149 cases, so the survivors had a low grade of malignancy. It is sensible to continue the method when of 6 patients with evident metastases in the pelvis 2 have lived five years and are apparently well. We think that where there are general metastases the disease recedes to some extent for a few months.

It is also possible to make apparently inoperable tumors operable by giving x-ray treatment first, as shown by Baer and others.

We believe that the peritoneoscope may be of value in the diagnosis of early cases, but we find it difficult to obtain a view of the bottom of the pelvis. The most important factor in getting better results in this disease is earlier diagnosis, for we all know that most of the cases become incurable before definite symptoms arise. Preventive examinations may reveal the presence of small tumors and treatment may be instituted early, but there are evidently cases with an everted type of papillary cancer which spread across the pelvic peritoneum without forming a palpable tumor. There is a sense of thickening to the trained examiner, and the patient sometimes complains of a vague discomfort or feeling of pressure in the pelvis. The peritoneoscope should reveal such growths, and treatment by operation and x-ray should be started early enough for some cures. The peritoneoscope is useful in discovering the extent of the disease. We have the feeling that because such a large percentage (47 per cent) die within the first two years after operation it might save a patient a useless operation and convalescence if she were not operated upon if the peritoneoscope showed generalized metastases

Apropos of the question of the omentum, two years ago I operated upon a woman with a pseudomucinous cyst with gross malignant change in many places. The omentum was carcinomatous and three or four inches thick. I removed the tumor together with other pelvic organs but left the omentum in situ. I saw the woman again last week and she was clinically well. The omental mass had shrunken so that it could not be palpated abdominally. One wonders if her omentum had not been there whether the intestines would have been involved as the omentum was, in which case she would have had a chance of an obstruction. The disappearance of this omental mass after removal of the parent tumor emphasizes the point made by Dr. Pemberton of the advisability of removing the tumor grossly even when one obviously cannot remove every bit of the neoplasm.

I should like to mention finally three very illuminating cases of granulosa cell tumor which recurred thirteen, sixteen, and twenty years after the original operation. In all three cases we have biopsies of the recurrent tumors, and in each instance, the microscopic picture of the recurrent tumor is identical with that of the original growth. Five-year "cures" of granulosa cell tumors do not by any means indicate a permanent cure.

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—Dr. Pemberton's figure of 32 per cent cure is not only very encouraging, but is actually one of the best ever reported on any considerable number of cases of ovarian cancer. On the other hand, I am more or less convinced that any such figure requires careful scrutiny.

Ovarian carcinoma is such a miscellaneous group that it is probably incorrect to report on it as a whole. In this respect Dr. Pemberton has made a real contribution in separating the granulosa cell tumors from his series. There is, however, another group of tumors where inclusion or exclusion will largely affect the end result figures. There are a large number of tumors on the histologic borderline between the benign papillary cystadenomas and the malignant cystadenocarcinomas, and in our experience it is in this group that most cures of so-called cancer of the ovary are found.

In spite of several opinions expressed today to the contrary, grading to the extent of recognizing this type of questionable malignancy is of vital importance in prognosis and statistics. You are familiar with the cystadenoma which produces implants that eventually disappear. This type is morphologically quite similar to the adenoma malignum of the endometrium which experience shows should be classed as cancer. A similar tumor in the ovary has, however, almost always a benign course.

It is of vital importance then in interpreting statistics on carcinoma of the ovary to know what histologic standards have been set by the writer.

Our own experience at the Roosevelt Hospital in New York illustrates this point. In 1929 we reported about 8 per cent of five-year cures. We went over the new material a year ago, accepting at first the pathologist's routine diagnosis for classification, and found that with the recent cases the five-year cure rate had risen to about 25 per cent. When we reviewed the slides, however, we discovered that about 7 out of 10 new five-year cures were tumors of a high degree of differentiation and of doubtful malignancy. With these subtracted we were back to the old figure.

Until there can be some standardization of the histologic criteria of malignancy in the ovary, results obtained by different clinics or by rival methods of therapy cannot be satisfactorily compared.

DR. WILLIAM P. HEALY, New York, N. Y.—Until comparatively recently the operator has seldom waited for the opinion of a pathologist on the gross specimen before deciding to limit the removal to the adnexa of one side. If the adnexa are involved on both sides, of course, we do not need to wait for that opinion but with one side apparently normal it is our custom to send the total specimen to the pathologist or have him present as consultant, so that we will know immediately what operative procedure is indicated. Often we have patients sent to us after a previous operation in which only one side has been removed, but within another year or so the other side has become involved.

Röntgen ray is the only form of therapy we can use, aside from surgery. Radium is of little value unless used in a pack and that is not a very facile form of

has been largely with autopsy material most of the deaths have been due to intestinal obstruction. Consequently, my own feeling at the moment is that unless the omentum is involved at the time of operation it is better left in situ.

As to treatment, obviously surgery, immediate and as completely radical as is feasible, in every instance in which carcinoma of the ovary is diagnosed or suspected, is the primary indication. Thereafter the patient should receive the maximum of irradiation, which is even more important than the surgery.

Our technique with the radium bomb consists in the administration of 40,000 mg. hours to each of four pelvic fields, for a total of 160,000 mg. hours with 1 mm. of platinum filtration at 10 cm. distance. X-ray therapy is carried out on the 200 kv constant potential machine with Thoraeus filtration (equivalent to 2 mm. copper), 2,000 r. units being administered to four pelvic fields for a total of 8,000 r. units, measured on the skin.

In conclusion, I regret to announce that in the last five-year group we have only one authentic survival, both in our tumor clinic and in the private practices of the sixteen men in our department.

DR. EMIL NOVAK, Baltimore, Md.—The particular value of Dr. Pemberton's study lies in the fact that he has eliminated from his group certain types which are of relatively low malignancy. These include particularly the rather frequent granulosa cell carcinoma, the less frequent dysgerminoma and the rare arrhenoblastoma. Any series which includes any considerable number of this group should show much better results than pertain to ovarian cancer in general. Dr. Pemberton has avoided this error.

I was rather surprised that he classed only six of his 140 cases as solid carcinoma, and I presume that this must be due to the fact that his rather large group of "semisolid" tumors must include any solid neoplasms which have undergone cystic degeneration, and become in that sense semisolid. Strictly speaking, however, they should be grouped as solid carcinomas, which in the figures of most laboratories would be about two-thirds as common as the cystic variety of ovarian cancer. The whole question of ovarian tumor classification is still very confused, and it might be a fine thing for this Society to devote one of its sessions some time to a discussion of this subject, in an effort to arrive at some sort of satisfactory working classification.

I was particularly interested in one of Dr. Pemberton's slides because it illustrates what I believe to be the usual channel of spread of ovarian cancer to the endometrium. This slide showed an intact endometrium, and immediately beneath it a carcinoma nest in a lymphatic. Such a small carcinoma area is likely to destroy and replace the overlying endometrium, so that it might give the impression that carcinoma particles have implanted themselves on the uterine mucosa. While this is a theoretical possibility, I believe that it is far less common than the lymphatic route of dissemination.

With reference to the matter of histologic grading, it would seem to me to be expected that this would be less valuable with the varied group of ovarian cancers than in the evaluation of tumors of one histogenic type. Ovarian cancer is of multiple and in most cases unknown histogenesis, so that systems of grading might be expected to be of comparatively little value in the present state of our knowledge.

Dr. Pemberton's suggestion concerning removal of the omentum would seem a wise one when the omentum extends into the pelvis, or when it is adherent to the ovarian tumor. On the other hand, where the omentum is very short and in the upper abdomen, this procedure would not seem essential.

DR. RICHARD W. TE LINDE, Baltimore, Md.—There is no field in gynecology in which the prognosis is more uncertain than in ovarian tumors. This is true both from the clinical standpoint and from the standpoint of microscopic pathology. Ten years ago I saw a woman with a massive recurrence of an ovarian neoplasm, and it seemed that it would be but a short time before she died. She was given deep x-ray therapy, and I saw her a month ago clinically well with complete absence of the pelvic mass. The tumor corresponded microscopically to Schiller's so-called mesonephroma. I wonder whether all of this special group of tumors which we now recognize as an entity will prove to be so radiosensitive.

CANCER OF THE VULVA*

AN ANALYSIS OF 155 CASES (1911-1940)

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

IN STUDYING the clinical aspects and methods of treatment of a disease that is as relatively infrequent as cancer of the vulva, the observer whose experience is limited to less than twenty cases can hardly venture on an opinion. My first paper written in 1917 was based on only 15 cases. In the course of the succeeding years from my service at the Barnard Free Skin and Cancer Hospital and in private practice that number has now increased to 155, a total which compares favorably with the reports from larger clinics in this country and abroad and justifies, I believe, some, rather definite conclusions as to etiology, incidence of gland metastasis, and the relative value of radiologic and surgical methods of treatment.

These cases may be divided into five-year periods as shown in Table I.

TABLE I

1911-1915	8 cases
1916-1920	19 cases
1921-1925	26 cases
1926-1930	31 cases
1931-1935	27 cases
1936-1940	44 cases

I have not included in this series of 155 cases, 3 cases of sarcoma of the vulva and one early case of melanoma situated in the pubic region. Three other cases of melanoma originating about the labia and urethral meatus have been included. Twelve cases of periurethral cancer were also classified as vulvar lesions since the exact point of origin of the neoplasm could not always be determined, especially in the more advanced cases. In one patient the small labial tumor proved to be an adenocarcinoma, probably of sweat gland origin. With the exception of three adenocarcinomas springing from Bartholin's gland, the remaining tumors were carcinomas of squamous cell type. The histologic picture varied greatly. Elsewhere the histopathologic changes in these cases will be more fully discussed. Suffice it to say that the lesions varied in malignancy from small well-differentiated papillary nodules in which a positive diagnosis could only be established after careful study, to tumors in which the loose-structured undifferentiated appearance of the tumor cells resembled the picture of a sarcoma. The former relatively benign lesions usually originated from the skin of the labia or prepuce; whereas the more malignant lesions usually arose from old syphilitic vestibular ulcers or from the glans of the clitoris. Cancer of Bartholin's gland occupied a more intermediate position.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

application. We feel that high voltage roentgen ray is better because it can be spread over a larger area and more tissues can be included. X-ray therapy is usually a palliative rather than a curative measure. Yet if we believe from the physical examination of the patient that the lesion is carcinoma of the ovary, the patient is subjected first to preoperative roentgen irradiation rather than to operation first followed by postoperative irradiation. The results are much better if the irradiation is used first in the majority of instances.

DR. FRED L. ADAIR, Chicago, Ill.—Dr. Taylor has emphasized that we must be extremely careful in evaluating statistics on curability. There is great difficulty first in interpreting the histologic picture and deciding whether it is or is not malignant in certain of these cases. Second, because we are frequently dealing with a very large tumor from which a small area is selected for microscopic examination, we may miss an area which is malignant.

DR. PEMBERTON (closing).—Since the publication of the program, I have done much more work on the paper. There are 149 instead of 122 cases and the five-year salvage is 32 per cent instead of 22 per cent.

Grading depends largely on a personal equation. There is such a multiplicity of etiology in these tumors, as Dr. Novak says, and they vary so much in their histology that I do not believe you could have a real standard that would work in several different clinics.

It is also true that 69, or 47 per cent, of these patients died within two years after the original operation. Hence I wonder whether it is worth while to operate on patients who have general abdominal metastases? We have not tried preoperative x-ray treatment.

As to the omentum, my idea was that it might have microscopic metastases in it. I agree also that most of these patients die of intestinal obstruction, and it is not so important whether you leave it in or remove it. It might be better to leave it in if it appears normal, but certainly if there is any suggestion of metastasis it would be better to remove it.

As to irradiation, we start three weeks after the operation and do not irradiate patients in poor condition because the toxemia they get from it may tip the scales.

As to the semisolid tumors, I call the adenomatous ones with solid masses in them semisolid, and the medullary ones are solid. Here again is a personal classification which is difficult to define.

These tumors are silent and sometimes do not cause symptoms until they are quite far developed. In our series 36 per cent were incurable when first seen. Preventive examinations are necessary in order to make early diagnoses, but in all of the preventive examinations I have done, I have found only one ovarian tumor and that was in a woman who came in a year after a negative examination, and who had at that time a benign serous cystadenoma.

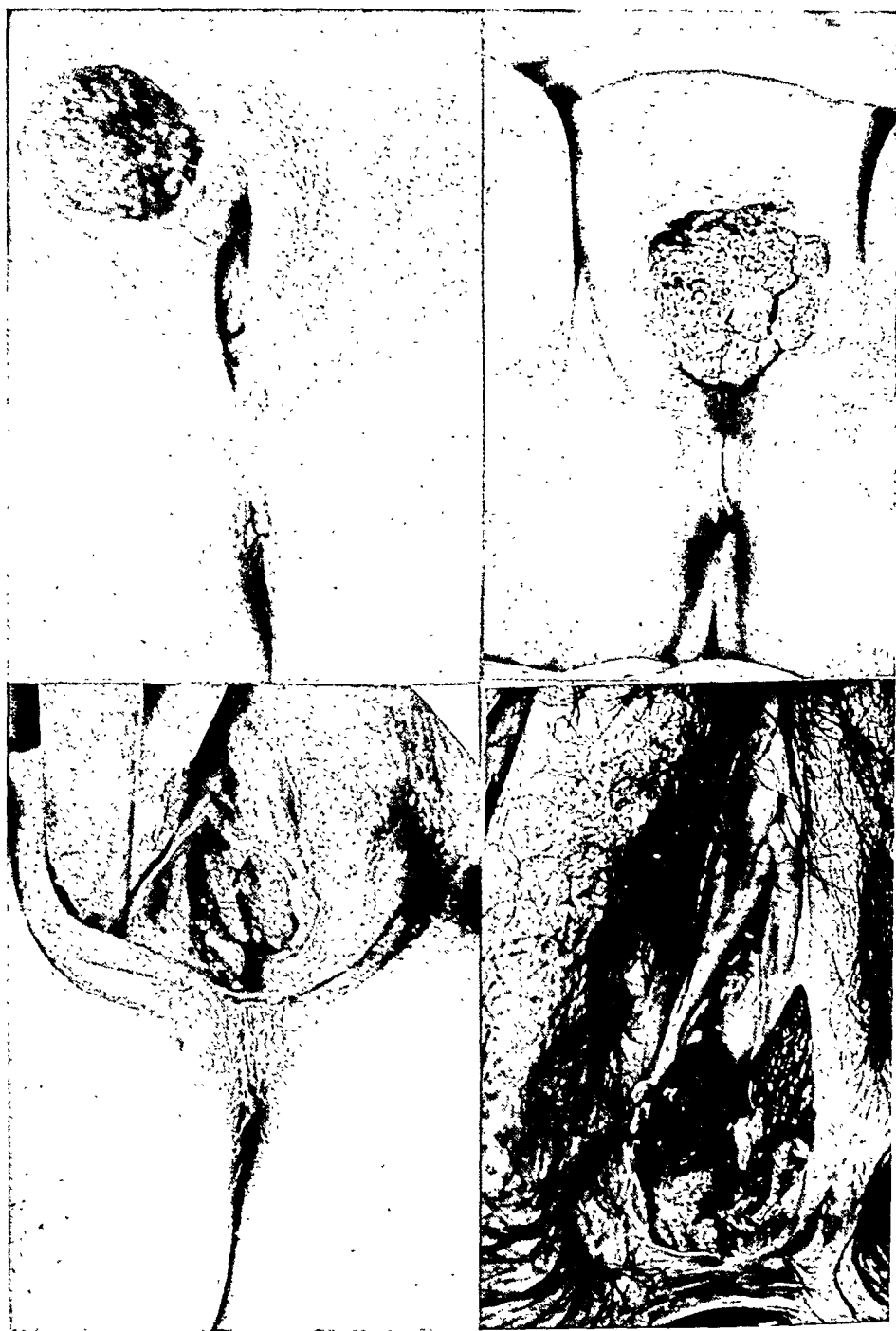
As regards grading, Dr. Taylor suggested that most of the survivors were probably in Grade I. This proves to be true, for 26 (70 per cent) were graded at I, 10 (27 per cent) at II, and only one (3 per cent) at III. This last patient died in the sixth year after operation for cancer. Therefore the degree of malignancy plays a part in the prognosis; but here, as in cancer of the cervix, the gross extent of the disease is the usual determining factor.

MULTIPLE CANCERS

Of special interest in the analysis of this group of cases is the relatively high incidence of double cancers. I have not included under

A.

B.



C.

D.

Fig. 1.—A and B show epidermal carcinoma of the vulva on a basis of leucoplakic vulvitis; C, case of periurethral carcinoma; D, vestibular carcinoma on a syphilitic basis.

From an anatomic viewpoint I have tried to separate the 155 cases according to site. Some writers had differentiated between labia minora and majora, perineum, and clitoris. In Table II, I have preferred to include under one head as epidermal, the entire vulvar skin including the prepuce. As stated in previous papers, many cases of typical preputial cancers are called clitoris cancer. Almost always such tumors start from an area of preputial leucoplakia and not from the clitoris itself although the latter may be secondarily involved. True clitoris cancer is very rare. Besides the group of periurethral and Bartholin gland cancers, we have cases springing from the more delicate epithelium of the vestibule of the vagina. Table II shows this anatomic subdivision of cases:

TABLE II

Epidermal	104 cases
Vestibular	11 cases
Periurethral	12 cases
Bartholin gland	9 cases
Glans clitoris	2 cases
Unclassified (advanced cases)	17 cases

Coming now to the important question of lymph gland metastasis in carcinoma of the vulva, we find that in 88 out of the 155 cases observed there was evidence of carcinoma either in the form of large hard fixed glands in the advanced inoperable cases or in microscopic evidence of such metastasis in those patients subjected to a partial or complete excision of the lymphatic chain. This would make 57 per cent of the total cases. With the certainty that a certain number of smaller metastases are doubtless overlooked when serial sections of all glands are not made, it seems fair to reiterate a statement previously made that approximately two-thirds of vulvar cancers are complicated by lymph gland metastasis.

When we list only the cases subjected to lymph gland removal, we find the incidence of metastasis somewhat lower. In the group of one-sided incomplete or superficial gland operations, we note that in 18 out of 27 such instances (66.6 per cent), cancer was present microscopically. In the less advanced cases subjected to a complete Basset operation, cancer was found present in only 28 out of 68 cases, an incidence of 41 per cent. Adding these two groups of operative cases together we find:

Carcinoma present in glands	46 times
Carcinoma absent in glands	49 times
Percentage of cancer metastasis	48.4

Extension of the disease to more distant lymphatics was relatively infrequent. However a considerable number of the terminal cases showed involvement of the lungs, the abdominal organs and even in one case the brain. Unfortunately relatively few of the terminal cases died in hospitals where an autopsy could be secured. Hence, the information on this point has but little value.

the appearance of the vulvar carcinoma. In each instance the possibility of interpreting these cancers as metastasis was carefully eliminated.

Cancer of the cervix, 3 cases (2 before, 1 after vulvar carcinoma)

Cancer of the breast, 2 cases (1 before, 1 after vulvar carcinoma)

Cancer of the head and neck, 5 cases (3 before, 2 after vulvar carcinoma)

In a recent communication read at the meeting of the American Society for Cancer Research, Shields Warren analyzed the cases of multiple malignancies from several Massachusetts institutions and found that in a series of 1,149 cases of cancer of the skin, there were 77 patients, who at some time showed evidence of cancer in other organs of the body. This incidence of 6.7 per cent was over twice as high as the normal expectancy, 3.1 per cent, of such a combination of the two cancers. The occurrence of 10 such double cancers in 155 vulvar malignancies, or 6.4 per cent, in my series corresponds rather closely to Dr. Warren's figures. The development of a satisfactory statistical formula to express accurately the difference between the expected and actual incidence of multiple cancers in this vulvar group is difficult because of the small total number of cases involved. Clinical observations such as these, however, point to an important somatic factor in the causation of cancer.

GENERAL STATISTICS

Age.—The average age of the 155 women in this group was 58 years. This is slightly less than the 60.9 years recorded by Folsome in his recent report of 126 cases from the University of Michigan clinic. When we analyze this age incidence more closely, however, we find in our series that 88 patients were over 60 years of age and only 67 were under 60. Table III shows patients grouped by decades.

TABLE III

24-29 years	4
30-39 years	17
40-49 years	23
50-59 years	23
60-69 years	54
70-79 years	31
80-87 years	3

The oldest patient was 87 years, the youngest 24 years. A highly malignant sarcoma of the vulva not included in this series was found in an infant five months old.

The age incidence of the five-year survival cases was 55 years, indicating that the malignancy of the disease does not decrease with the age of the patient. All 12 operative deaths in this series of 155 patients occurred in women over 60 years, with an average age of 68 years.

Symptoms.—Pruritus was noted as the outstanding symptom which caused the patient to come for examination in 42 cases. In many other instances, it was also noted but in addition to this the occurrence of a lump or an ulcer or sore was the primary reason for the patient's consultation. A bloody discharge or burning on urination was occasionally stated as the outstanding symptom. Table IV shows the frequency of these symptoms.

Duration of Disease.—In no form of genital cancer do we find more evidence of inexcusable delay in seeking medical advice than in cancer of the vulva. This delay is only too often increased by failure in diagnosis or improper advice on the part of

this head four cases in which a new cancer appeared many years after excision of the primary tumor upon a remaining island of leucoplakic skin. These were all patients in whom a cancer had developed on the basis of a leucoplakic vulvitis with kraurosis. The primary tumor was



Fig. 2.—A and B are examples of carcinoma of Bartholin's gland; C and D are cases of primary carcinoma of the glans clitoris.

either on the prepuce or the upper labial region. The vulvectomy did not include the perineoanal region, and the new cancer usually developed in this area on a leucoplakic area as a superficial lesion and not in the vulvar scar. In addition to such local new cancers, we find the following incidence of cancer in other organs, either before or after

I am convinced that we have been very remiss in our preventive measures in the past. The incidence of vulvar carcinoma might very possibly be cut in half, if we would adopt the following measures:

1. A complete vulvectomy in cases of well-developed leucoplakic vulvitis, and rigid supervision, at least twice a year, in milder cases where the patient refuses operative treatment.

2. Intensive antisyphilitic treatment in tertiary lesions of the vulva, especially in negroes.

3. Removal of vulvar warts in women past the menopause.

4. Close observation or excision of enlarged Bartholin glands in women over 40 years of age.

5. Cautery excision or radiant treatment of urethral caruncles.

Particularly in leucoplakic vulvitis would I stress the advantages of surgery over nerve resection or treatment with ovarian hormones. The latter undeniably often decreases the pruritus, but the question whether the use of such carcinogenic substances may not at times predispose to the development of a cancer might very well be raised.

In connection with the relationship of leucoplakic vulvitis and cancer, I would cite three interesting observations, one of which comes from the practice of Dr. W. P. McNalley, to whom I am indebted for the privilege of using it.

CASE REPORTS

CASE 1.—Mrs. Y. G. had had symptoms of vulvar itching with skin changes that had been treated by a dermatologist twelve years ago when she was 67 years old. Ten years later she was seen by a gynecologist, the condition was diagnosed as leucoplakic vulvitis, but because of her age and a cardiorenal condition, anesthetic salves alone were prescribed for the relief of her pruritus. At this time the vulva showed the typical picture of a leucokraurosis without any ulcers or suspicious thickening anywhere. Fifteen months later, she noticed a small lump which slowly increased in size in the following nine months. When I was called in consultation by her physician, Dr. Leon Foster, she had an elevated plaquelike cancer 4 cm. in diameter in the right labial region with a parchmentlike leucoplakia of the entire vulva. Since she was then 79 years old and had a bad heart, a simple vulvectomy was done. Her immediate condition was good, but she suddenly died on the fourteenth postoperative day of coronary embolism.

CASE 2.—Mrs. M. S. was operated upon by me at the age of 60 years for a leucoplakic vulvitis of long standing. A vulvectomy was done, but the pruritus returned one year later at a point just beyond the area of skin removed. Unfortunately the patient did not return for re-examination as she had been instructed. She was not seen from Sept. 30, 1930 until Nov. 25, 1936. By this time she had developed an epithelioma 4 cm. in diameter in the right labial region with evidence of leucoplakic change about it and the perineal region. The radical vulvectomy and double-sided Basset lymph gland removal was followed by a severe local infection, aggravated by an acute cholecystitis, and death occurred fourteen days after operation.

CASE 3.—Mrs. K. M. (private patient of Dr. McNalley) consulted him in June, 1935, for pruritus vulvae. On Oct. 29, 1935, a vulvectomy was done for a typical leucoplakic vulvitis. Microscopic examination at this time showed no evidence of cancer. In March, 1936, she was entirely well. She did not return for further observation until July 25, 1938, when examination showed a tumor 6 cm. in diameter in the right labial region rising from a remaining island of leucoplakia. The inguinal glands on the right side were enlarged and hard. A right-sided Basset

TABLE IV

Lump in vulva	46
Pruritus	42
Sore on vulva	26
Burning on urination	24
Blood-tinged discharge	22
Insufficient data	4
Counted twice	9

the family doctor. It is to be hoped that cancer educational work may in the future be extended to include this form of malignant tumor. Here are the figures of the interval between onset of symptoms and competent medical advice. I have not included, as a part of this elapsed time, cases in which a leucoplakic vulvitis had existed for many years previous to the development of the cancer.

TABLE V

Less than three months	7 cases
3-6 months	48 cases
7-12 months	24 cases
13-24 months	34 cases
Over 2 years	24 cases
Insufficient data	18 cases

Were it not for the fact that cancer of the vulva is of relatively slow growth as compared with cervix or vaginal cancers, few cases would be curable.

I was amazed to find on analysis of these 155 cases how many patients had tried pastes or salves or had been given inadequate surgical or radiologic treatment before coming to us for advice. Thirty-one such instances were noted (20 per cent of the total). In 22 patients a local excision of the nodule had been made, three times in combination with an inadequate radium or x-ray treatment. In 4 cases radium or x-ray was alone applied. Twice the nodule was cauterized. In two other cases caustic pastes or salves were applied and one patient tied a string around the pedicled tumor. In spite of all this preliminary malpractice, it was surprising that we succeeded in obtaining 7 five-year survivals in this group.

Etiologic Factors.—In previous reports I have discussed more fully the etiologic factors that may possibly predispose to the development of cancer of the vulva. In many instances the extent of the disease makes it impossible to put our finger on the underlying factors of local irritation, but, all in all, the presence of a preceding pathologic condition is very common as shown in Table VI.

TABLE VI

Leucoplakic vulvitis	72
Syphilitic or postsyphilitic ulcer	9
Senile warts	6
Bartholin abscess	4
Urethral caruncle	3
Trauma	3
No definite pathology	58

Of undeniable importance is the occurrence of a leucoplakic vulvitis in almost one-half of the cases. It was an underlying factor in 72 out of 104 cases of epidermal cancer. A pre-existing syphilis was noted in 9 out of 11 vestibular cancers. Bartholin infection was definitely noted in 4 out of 9 Bartholin gland tumors.

PREVENTION

What has been stated regarding etiologic factors raises the issue: How often can we prevent the development of a cancer of the vulva?

the extent of the disease in the particular case. Surgical measures were employed in all but 38 of the 155 cases. Radium and x-ray were early employed in some cases but in recent years have been almost wholly abandoned, owing to unsatisfactory results and painful sequelae. Table VIII shows the division of cases according to the therapeutic measures employed.

A.

B.



C.

D.

Fig. 3.—A, Group I carcinoma of the vulva; B, Group II infiltrating carcinoma of the vulva; C, Group II epidermoid cancer of the prepuce; D, Group III cancer of the left labia.

operation was done and radium applied locally. The inguinal glands showed cancer. There was rapid extension of the disease and the patient died three months later.

Cases such as these teach the lesson, I think, that patients with leucoplakic vulvitis, even if operated upon radically, should be kept under close observation throughout their life and warned to return on the slightest appearance of an ulcer or lump. The close etiologic relationship between this condition and cancer is certainly emphasized by such reports as these.

Stage of the Disease.—The classification of cases according to the stage to which the cancer has progressed is of value in determining the indication for, and the results of, treatment. D. den Hoed puts cases that are recurrent after previous treatment in a special class, but in view of the reasonably favorable results obtained by him and by myself in this group, I cannot see that it has any special value. The following classification seems practical:

Group I: Patients without palpable metastasis, tumor 1 to 3 cm. in diameter.

Group II: Patients without palpable metastasis, tumor 4 to 7 cm. in diameter.

Group III: Patients with tumor over 7 cm. in diameter, or smaller tumors with evident but still movable metastasis.

Group IV: Patients with extension to the vagina or subpubic space or with large fixed lymph glands.

Group V: Far-advanced cases with broken down lymph glands and cachexia.

The determination of lymph gland metastasis is not easy of diagnosis before operation. In practically every case, a few enlarged lymph glands can be felt in the groin. Only when they are over 3 cm. in diameter and hard can we say with reasonable certainty that a metastasis is present.

Analysis of the 155 cases in my series according to clinical groups is given in Table VII, together with a similar analysis made of the 128 cases reported by Folsome from the University of Michigan clinic.

TABLE VII

TAUSSIG			FOLSOME		
GROUP	NUMBER	PER CENT OF TOTAL	GROUP	NUMBER	PER CENT OF TOTAL
I	28	18	I	10	8
II	48	31	II	22	17
III	43	28	III	40	31
IV	29	18	IV	43	34
V	7	5	V	13	10
Total	155			128	

From these figures it would seem that Folsome's cases were somewhat more advanced than mine, which may in part account for the lower survival rate in his series.

TREATMENT

In the course of the years from 1911 to 1940 certain changes have occurred in the method of treatment, but on the whole a fairly consistent plan has been observed in the past two decades varied only by

TABLE VIII

Complete Basset operation with vulvectomy	68
Incomplete or superficial gland removal with vulvectomy	27
Vulvectomy	22
Radium or deep x-ray therapy	22
Palliative measures	7
Refused treatment	9
	155

rule 70 per cent of cancers of the vulva are surgically operable. If we consider only the epidermal cases this percentage would be considerably higher.

OPERATIVE MORTALITY

The mortality varies primarily with the age and physical condition of the patient rather than with the extent of the operation as seen in Table IX.

TABLE IX

	CASES	DEATHS	PER CENT
Complete Basset with vulvectomy	68	5	7.35
Incomplete gland removal with vulvectomy	27	3	11.1
Vulvectomy only	22	4	18.2

The higher mortality in vulvectomies was due primarily to the age incidence. The average age of the four women who died after vulvectomy was 72 years. Even more striking are the figures in the cases where a complete Basset operation was done. Out of 45 Basset operations in which the patient was under 65 years, there was only one death (2 per cent); whereas in the 23 Basset operations done on women over 65 years, there were four deaths (18 per cent). This clearly shows that any surgical procedure, and especially the extensive Basset operation if done in such extremely old women, is bound to be attended by a high mortality. In the 5 operative deaths following the Basset operation, the cause was: pneumonia, 3 cases; pulmonary embolus, 1 case; septic infection with cholecystitis, 1 case.

Basset Operations.—This radical, double-sided, lymph gland removal with vulvectomy was done in 19 out of the 28 Group I cases, in 31 of the 48 Group II cases, in 17 out of the 43 Group III cases, and in one Group IV case. The reason for not doing more Basset operations in the Group I and II cases was partly because of the physical condition of the patients, and partly because for many years my service at the Barnard Free Skin and Cancer Hospital was shared by Dr. Gellhorn, who pre-

TABLE X

	CASES	CANCER IN GLANDS	PERCENTAGE INVOLVEMENT
Group I	19	4	0.21
Group II	31	13	0.42
Group III	17	10	0.59
Group IV	1	1	
Total	68	28	0.41

Although 117 of the 155, or 75.5 per cent, were subjected to surgical excision of the tumor with or without the tributary lymph gland chain, this hardly represents a true picture of the operability, since, in a certain number of the vulvectomies, the procedure was definitely merely



Fig. 4.—A, Group IV vulvar carcinoma with indurated adherent gland in right inguinal region; B, Group IV labial cancer with extension to the perirectal and subpubic space; C, Group IV cancer of the vulva with extension up the vaginal canal; D, Group V cancer of the vulva with large necrotic adherent lymph gland metastasis.

a palliative procedure. I am convinced, however, that many surgeons have in the past considered cases inoperable that in our experience are not only technically removable but even give a fair chance for a five-year survival. I think it therefore no exaggeration to say that as a

tion of a firm compression bandage over the inguinal wound so as to eliminate as far as possible dead spaces with the tendency to retained secretions. Only in rare instances have I been able to secure primary wound healing. Varying changes of technique have failed to prevent the frequent occurrence of necrosis in the wound edges associated with a moderate wound infection. This has, I find, been the general experience of other operators and is doubtless due largely to the poor vitality of tissues in this region in older individuals.

In the technique of vulvectomy, I have stressed a wide excision of the vulva, including all the perineal skin in cases associated with leucoplakic vulvitis. Attempting to close this large defect by skin flaps from the thighs has proved impractical, owing to poor wound healing. Hence, I have usually left a considerable defect in the vulvar wound to be closed by granulation. The perineal defect can, however, be readily covered with a posterior vaginal flap. The vulvectomy is best done with the diathermy knife and the wound edges subsequently trimmed off with the scalpel. In a few cases of urethral or subpubic involvement, radium has been placed in the open wound or urethra for a suitable dosage. The postoperative wound is exposed to light and kept as dry as possible to prevent maceration.

One of the complications of this extensive procedure has been the length of time required for the operation. Local anesthesia, occasionally supplemented by small amounts of ether narcosis, has usually been employed to diminish operative shock. Some time has been saved in the inguinal dissections by dividing my assistants into two teams, one working on each side. In 37 instances the operations were done in one stage (usually early cases), and in 31 patients a two-stage operation was done. In not a single case did the operative death occur earlier than the sixth day after operation.

In the after-care we would stress measures to secure proper drainage of the inguinal wounds, and the early establishment of a semi-Fowler position of the body to diminish the chances for pneumonia. When sloughing has occurred, the wound edges should be trimmed; and after clean granulations have been formed, pinch grafts should be taken from the thighs to produce epithelialization of the wound defect.

Five-Year Results.—To obtain a five-year survival in carcinoma is always a source of gratification. From this viewpoint cancer of the vulva ranks next to cancer of the uterine body in the percentage of successful cases treated. Previous to 1935 there were 108 cases of vulvar cancer in my series. Seven of these refused treatment or went elsewhere. Of the 101 remaining cases, 32 survived a five-year period. Divided according to extent of the disease, these 32 cases were Group I, 9 out of 13 cases (69 per cent); Group II, 14 out of 35 cases (40 per cent); Group III, 9 out of 25 cases (33 per cent); and none of 28 Group IV or V cases.

If we divide these five-year cases according to the method of treatment employed, we find definite evidence of the value of the radical lymph gland resection.

TABLE XI

	CASES	NUMBER SURVIVAL	PERCENTAGE SURVIVAL
Basset and vulvectomy	41	24	58.5
Superficial or incomplete gland removal and vulvectomy	21	6	28.6
Vulvectomy only	12	1	8.2
Radiation treatment	21	1	4.8
Palliative measures (no excision or radiation)	6	0	0.0
Total	101	32	32.0

ferred to do a superficial or one-sided gland removal in cases of vulvar carcinoma. Lymph gland metastasis in relation to the various groups in Basset operations was as shown in Table X.

Points in Technique.—Originally I followed closely the method described by Basset including a single incision from one iliac spine to the other and including the entire vulval mass. Also I routinely cut both Poupart's ligaments to gain access to the area in the femoral ring. In the course of the past twenty years, I found that the complications of wound healing with wide separation of the wound edges made it desirable to make three incisions, one over each groin and one over the vulva, retaining a bridge of normal skin between them to prevent too wide a gaping of the postoperative wound. Retention of this bridge of skin did not lead to recurrence at this point. I also found that in all but a very few cases all lymphatic glands could be cleanly excised without actually cutting Poupart's ligament, hence this was omitted, as adding to the risk of hernia. Another important change was the angle

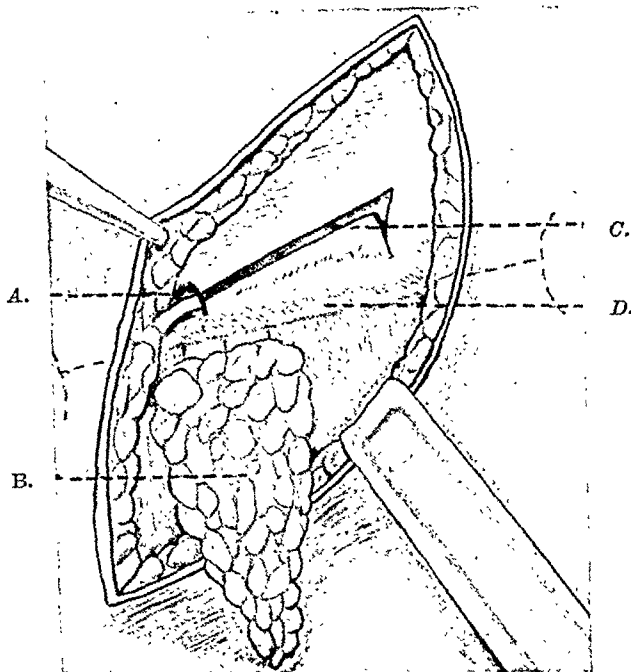


Fig. 5.—Right-angled fascial incision over the inguinal canal in Basset operation. A, External inguinal ring; B, superficial inguinal lymph gland mass dissected free; C, obturator internus muscle; D, Poupart's ligament.

of the inguinal incision. Instead of having it run almost parallel to Poupart's ligament, it is now being made at an angle of 60 degrees to this ligament, thereby aiding to preserve the nutrition of the edges of the inguinal wound. The incision goes as far as the lowest point of Scarpa's triangle, permitting the more complete removal of fat and lymph glands surrounding the deep saphenous vein. I have also extended the deep exploration of the obturator region, from which one or two good-sized glands are invariably excised. The additional removal of the hypogastric gland, as suggested by E. Kehrer, requires a far more extensive primary incision, and, considering the resulting higher postoperative mortality and the very rare involvement of this gland, does not seem justified.

Another change in technique which I have adopted is the right-angled cut through the transversalis fascia. This cut follows the course of the inguinal canal from the external inguinal ring to a point over the internal ring and then proceeds from there at right angles to Poupart's ligament. By turning down this fascial flap, access to the external iliac glands is more readily obtained.

The inguinal wounds are always drained, usually through a separate slab incision at the lowest point of drainage in Scarpa's triangle. Of importance is the applica-

CONCLUSIONS

1. Early recognition and prompt adequate treatment are extremely rare in cancer of the vulva. In spite of this the disease, because of its relatively slow growth, offers a reasonably good prognosis.

2. Prevention of carcinoma of the vulva by early excision of the leucoplakic vulva should materially lower the incidence of the disease.

3. Radiologic treatment of the disease gives disappointing results, and is usually attended by painful burns.

4. The complete modified Basset operation gives splendid results in patients with operable lesions (Clinical Groups I-III) who are under 65 years of age. In older patients only those in better than average physical condition with relatively early lesions should be subjected to this procedure.

5. Approximately two-thirds of the cases of cancer of the vulva are still operable at the first examination. In those in whom a Basset operation is done we can expect a five-year survival in about three out of five (58.5 per cent), even though two out of five (41 per cent) already show evidence of lymph gland metastasis.

3720 WASHINGTON BOULEVARD

DISCUSSION

DR. JOHN R. FRASER, MONTREAL, CANADA.—It is encouraging for me to know that this disease which we have always regarded as being most unsatisfactory from a therapeutic point of view, will under certain circumstances yield such excellent results after five years. It is true that the bulk of these cancers are skin cancers. The unsatisfactory ones, of course, are the vestibular lesions, the periurethral lesions, and the more rare Bartholin gland lesions.

Seventy per cent of these patients Dr. Taussig has been able to treat in a surgical manner. There remain 30 per cent who are beyond the scope of surgery. That is the first discouraging fact. The second is that these lesions occur in women even in the later decades where other disabling conditions make them uncertain surgical risks.

Dr. Taussig brought out some very important points. First, leucoplakia is found in a large percentage of these women and is a disease which can be cured surgically. Second in cancer of the vulva there is a high incidence of metastases which are not clinically discernible. The latter is an important point in determining our procedure in the treatment of these lesions.

In our small group we have had since 1926 just 30 cases. Twenty-one of these are suitable for discussion from the standpoint of a five-year cure. Of these 21 cases, we saved 5, one being cured by radium, 2 by the use of electric cautery and surgery, and 2 by surgery alone. This simply shows that the best treatment so far as we have found is excision of the local lesion and a widespread removal of the gland-bearing tissue when the condition of the patient will stand it.

DR. KARL M. WILSON, ROCHESTER, N. Y.—I would like to present two rather interesting examples of rare vulval tumors which have been under my observation and which are of the melanotic type. The first case was in a far-advanced stage and the patient was dead two months after she came under observation.

The second patient, on the other hand, had had a melanotic tumor present two months before observation. She was 62 years of age and she was a diabetic and also an arteriosclerotic, therefore a rather poor surgical risk. We did a vulvectomy first and later, a resection of the glands on both sides. Seven years after operation she was in excellent condition. My experience with melanotic tumors is limited to those two cases. Call it a 50 per cent survival if you will.

A review of the literature confirms the statements made in previous papers that treatment by radiologic methods is very unsatisfactory. Stoeckel's compilation gives 12 per cent of five-year cures with radiation alone. Groeger, Reiprich, Ruppert, Stoeckel, and Kehrer give percentages of five-year cures by the use of radical lymph gland excisions with vulvectomy ranging between 36 and 47 per cent. Where only the superficial glands are removed, a compilation from several sources made by me totaling 149 cases showed a 16 per cent five-year survival.

A good illustration of the relative value of radium and surgery in cancer of the vulva was the case of a woman who had an early Group I lesion of the right labia on a leucoplakic basis. She was treated with radium and x-ray by one of the leading radiologists of this country. The tumor completely disappeared, only to re-appear at the original site eight months later. For seven months it continued to grow slowly. Then she came to me and I did a complete vulvectomy. Her age (71 years) and blood pressure contraindicated lymph gland excision. This operation was done two and one-half years ago and at the present time there is no evidence of recurrence.

A further analysis of the five-year survivals following the complete Basset operation reveals some interesting facts. If we divide the cases according to clinical groups, we find that all of the Group I patients remained free of recurrence.

TABLE XII

	CASES	CLINICALLY WELL	PERCENTAGE SURVIVAL
Group I	10	10	100
Group II	20	9	45
Group III	10	5	50
Group IV	1	0	0

It would seem as far as these relatively small figures can be used, that the presence of cancer metastasis was of less significance than the extent of the primary lesion. Data on this point were as shown in Table XIII.

TABLE XIII

	NO. OF CASES	FIVE-YEAR SURVIVALS	PERCENTAGE SURVIVALS
Gland metastasis present	19	10	52.6
Gland metastasis absent	22	14	63.6

Ten-Year Survivals.—With a disease such as carcinoma of the vulva, in which the age incidence is around sixty years, the average expectancy of life would be not over ten years more. Consequently it is not surprising that a considerable number of these women, although cured of their cancer, died of other conditions (pneumonia, heart disease, nephritis) before the ten-year period had been passed. For this reason a calculation of ten-year survivals has less importance than in cancer of the cervix or ovary. Out of 74 treated patients seen over ten years ago, 12 survived a ten-year period (16 per cent). Two of these patients had only a superficial gland dissection, with a ten-year survival of 12 per cent in the 17 cases in this group. Out of 24 patients subjected to a complete Basset operation over ten years ago 16 survived the five-year period and ten survived the ten-year period (41 per cent). Of the six who died in this second five-year interval, four had recurrences of the vulvar lesion, one died of a new cancer originating in the breast and one died of an acute influenza pneumonia. Of the 10 patients who survived the ten-year period, we find only 6 still living today. The four deaths in this group were due to: (1) late local recurrence of the disease; (2) a new cancer of the cervix appearing fourteen years after cure of the vulvar lesion; (3) apoplexy in a woman 87 years of age; (4) senility in a woman 85 years of age. The two patients who have survived for the longest period of time were operated upon 16 and 17 years ago, respectively.

CARCINOMA OF THE CERVIX AFTER SUPRAVAGINAL HYSTERECTOMY*

CHARLES A. BEHNEY, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, University of Pennsylvania, and Gynecologic Service, Radiologic Department, Philadelphia General Hospital)

THE material for this study was obtained from the records of sixty-seven patients in whom carcinoma of the cervix was recognized at some time after supravaginal hysterectomy had been performed for various indications. Forty-three of these cases, all white women, were observed on the Gynecologic Service of the University Hospital. The remaining twenty-four patients, fifteen of them white and nine colored, were treated in the Radiologic Department of the Philadelphia General Hospital.

From 1913 to 1939 inclusive, 910 patients with carcinoma of the cervix were admitted to the Gynecologic Service of the University Hospital. In this case series, the cancer was recognized some time after supravaginal hysterectomy had been performed in 43 patients, an incidence of 4.7 per cent. In the second series, which comprised the 1,117 patients who had been admitted to Philadelphia General Hospital since the establishment of its Radiologic Department, in 1922, supravaginal hysterectomy had been carried out prior to the diagnosis of cancer in 24 cases, an incidence of 2.15 per cent.

Age.—The youngest of these patients was thirty-two years of age, and seventy-six was the age of the oldest in the series (Table I). The age distribution of the entire group varies little from that observed in patients with "cervix" cancer when the fundus of the uterus is present.

Previous Operation.—The most frequent indication for hysterectomy was fibromyoma uteri (Table II). Pelvic inflammatory disease was the indication second in order of frequency. Both of the patients who had been hysterectomized for carcinoma of the fundus had epidermoid carcinomas of the retained cervixes. Three instances of hysterectomy for carcinoma of the fundus, followed by adenocarcinoma of the stump, were not included in this study.

Initial Symptom.—The initial symptom most commonly elicited was bleeding (Table III). This was reported by 51 of our patients, or 76 per cent. Rarer first symptoms were loss of weight, irritating discharge, and pain. The single instance in which no initial symptom was reported was a case discovered at the time of the hysterectomy, by biopsy of a clinically undiagnosable lesion of the cervix. Prompt radiologic treatment was given and this patient is still living and well after more than five years.

Degree of Involvement.—To avoid minute subdivisions, lesions corresponding to Stages I and II, Schmitz's classification, were grouped together (Table IV). There was little difference in the end results obtained in Stages I, II, and III. This may have been due to the small number of cases studied, but we are of the opinion that it indicates greater difficulty in grading carcinoma of the cervix after the fundus has been removed than when no uterine trauma has preceded. No patients whose disease was in the fourth stage survived five years.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, Seignior Club, June 17 to 19, 1940.

DR. BENJAMIN P. WATSON, NEW YORK, N.Y.—It has been my experience that one of the early symptoms of cancer of the vulva is pain in the ulcerated lesion, and also tenderness in handling that lesion. It has in fact been my teaching to the students that whenever they find any ulcerative condition of the vulva which is painful or tender, they should immediately suspect carcinoma.

DR. TAUSSIG (closing).—Bartholin gland tumors, in my experience, are almost as favorable as the epidermal type. We have 3 patients who have passed the five-year period in our series.

As to the operative deaths, the immediate shock from the extent of the operation has not been a factor in our primary mortality. None of the five patients that died as a result of the Basset operation died earlier than the sixth day. Of course, there was toxic absorption and occasional infection due to the size of the wound, but the immediate operative mortality was nil.

I do not think that it is quite correct to say that vulvar cancer is comparable to cervix cancer in regard to its five-year cure rate. Thirty-two per cent in our total series is not a fair basis for comparison, since many of these cases in the earlier years were insufficiently treated. The important thing is that in the Basset type of operative treatment, which is utilizable in 70 per cent of all cases, we can cure approximately three-fifths of the cases, which is certainly far better than we can expect in cervix cancer.

Three patients with melanoma were included in this series and they all died. I have one patient with melanoma of the mons veneris who remained well for seven years.

As to the symptom of pain in the vulva, I should have included that under the heading of ulcer as a symptom. All ulcers about the external genitals are painful, and perhaps soreness of the vulvar region might have been a better term to apply than ulceration.

As to the use of x-ray, we have found no advantage in that procedure and would rather discount the employment of such measures in addition to surgery, in view of our excellent results without x-ray.

TABLE V. HISTOLOGIC DIAGNOSES

TYPE	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Squamous cell carcinoma	13	23	7	43
Adenocarcinoma	1	8	2	11
Not recorded	0	13	0	13
Total	14	44	9	67

Cases without histologic diagnoses are all dead.

*Alive, less than five years after treatment.

TABLE VI. TREATMENT AND RESULTS (UNIVERSITY HOSPITAL)

NO. CASES	TREATMENT	5-YEAR SALVAGE
2	600 mg. hr. or less	0
7	1,000-2,000 mg. hr.	2
21	2,400-3,600 mg. hr.	5
6	Over 4,000 mg. hr.	3
2	1 Series (high voltage therapy)	0
1	Untreated	0
4	Alive, less than 5 yr.	
43	Totals	10

Best results were secured with moderately high dosages.

TABLE VII. TREATMENT AND RESULTS (PHILADELPHIA GENERAL HOSPITAL)

NO. OF CASES	TREATMENT	5-YEAR SALVAGE
2	Less than 1,000 mc. hr.	0
4	3,500 mc. hr.	0
8	2 Series H. V. T.	
	5,000 mc. hr.	4
2	2 Series H. V. T.	
3	3 Series H. V. T.	0
5	Untreated	0
	Alive, less than 5 years	
24	Totals	4

Best results were secured with moderately high, dosages.

kv.) roentgen therapy, and others had external irradiation without radium therapy. The latter were, as a rule, the more advanced cases. In recent years, vaginal applications of radium or radon were given at a distance of 1 cm. with filters equivalent to 2 mm. platinum. The best results were secured in those cases whose radium dosage was from 2,400 mg. hr. to 5,000 mg. hr.

Von Graef¹ suggested that carcinoma of the cervix discovered within one year after subtotal hysterectomy should be regarded as having been present at the time of the operation. Nuttall and Todd² proposed a two-year criterion. Considerable evidence has been presented^{3, 4} that the life history of "cervix" cancer may span a period of eight or more years, and we believe that the three-year interval suggested by Healy and Arneson⁵ is a fair index of the development of the tumor after the hysterectomy. On this basis (Table VIII), it is probable that 29 (43 per cent) of our patients treated more than five years ago, had carcinomas of the cervix when the supravaginal hysterectomies were performed. In two of this group, biopsies from suspicious cervixes, secured at the time of the hysterectomies, enabled early diagnoses and treatment. These are the only cases discovered less than three years after the hysterectomy who survived for five years. If none but the patients diagnosed three or more years after hysterectomy were considered, the five-year salvage would be 41.4 per cent.

TABLE I. AGE OF PATIENTS

AGE	NO. OF CASES
30-39 years	10
40-49 years	30
50-59 years	20
60-69 years	6
Over 70 years	1
Total	67

45 per cent in fifth decade. 74 per cent in fifth and sixth decades.

TABLE II. INDICATION FOR HYSTERECTOMY

DISEASE	NO. OF CASES
Fibromyoma uteri	39
Pelvic inflammatory disease	11
Myoma and pelvic inflammatory disease	3
Carcinoma of the fundus	2
Benign hemorrhage	1
Not stated	11
Total	67

Two patients hysterectomized for carcinoma of fundus later had epidermoid carcinoma of cervix.

TABLE III. INITIAL SYMPTOM REPORTED

SYMPTOM	NO. OF CASES
Bleeding	51
Loss of weight	4
Irritating discharge	3
Pain	3
No clear record	5
No symptom	1
Total	67

Case without symptoms was discovered unexpectedly by routine biopsy.

TABLE IV. DEGREE OF INVOLVEMENT AND SALVAGE

STAGE	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
I and II	4	3	4	11
III	10	13	3	26
IV	0	28	2	30
Total	14	44	9	67

Results in Stages I, II, and III were similar.

*Alive, less than five years after treatment.

Pathologic Diagnosis.—Squamous cell carcinoma was the type of tumor found in 78.5 per cent of the cases, in which histologic examinations of the tumors were made (Table V). Thirteen patients for whom no pathologic diagnoses were recorded were included in the series. None of these lived five years after treatment and the progressive course of their disease attested the accuracy of the clinical diagnoses. The salvage of the patients with squamous cell carcinoma was three times that of those who had adenocarcinoma of the stump.

Treatment.—Three of the women in this series were unsuitable for any treatment because of the widespread invasion of the cancer and their poor physical condition. The remainder were treated radiologically (Tables VI and VII). Most of them received contact radium, or its emanations, into the canal or across the split stump. Some of these were also given external irradiation by means of high voltage (200

TABLE XI. COMPARATIVE SALVAGE

	CASES IN SERIES	SALVAGE CARCINOMA CERVIX	SALVAGE "STUMP CARCINOMA"
Univ. Hospital	910	18%*	26%
Phila. General Hospital	1117†	5.8%	21%

Treatment of carcinoma of the cervix after supravaginal hysterectomy was essentially the same as for general carcinoma of the cervix in each hospital.

*Computed to 1931 inclusive.

†248 patients were not treated.

RESULTS

In Table XI one sees that the results secured by treatment of carcinoma of the stump in each hospital series were better than those following identical treatment, in the same hospital, of carcinoma of the cervix, regardless of whether or not the fundus was present. If only the cases discovered three or more years after subtotal hysterectomy were considered, the salvage would amount to 41.4 per cent. Furthermore, the salvage was 40 per cent in the group who received treatment within six months of the appearance of the first symptom. The very low salvage rate in the Philadelphia General Hospital series is attributable at least in part, to the advanced stage of the disease when most of the patients were admitted for treatment. Two hundred and forty-eight of the 1,117 patients seen in that hospital were unsuitable for any sort of treatment at the time of admission.

Post-mortem examinations were performed on 3 of the 10 patients who died in the Philadelphia General Hospital series. In one there were metastases to the liver and lungs. A second had metastatic nodules in the lung, and in the third, there was no evidence of extension of the disease beyond the pelvis.

TABLE XII. COLLECTED STATISTICS

	NO. CA. CERVIX	SALVAGE CARCINOMA CERVIX PER CENT	INCIDENCE "STUMP CARCINOMA" PER CENT	SALVAGE "STUMP CARCINOMA" PER CENT
Ward and Sackett ⁸	752	28.5	7.4	44.2
Scheffey ⁹	273	20.5	3.66	42.8
University and Philadelphia General	1,764	10.4	3.9	24.0
Healy and Arneson ⁵	2,600	24.0	2.6	14.0
Von Graef ¹	4,269		4.1	9.0*
Meigs ¹⁰	1,218		4.7	
Smith and Bartlett ¹¹	673		4.0	

In four clinics the five year salvage is twice as great in the "Stump" Carcinomas as in Carcinoma of the Cervix in general.

*Pertains only to 331 patients treated by irradiation.

Collected statistics are shown in Table XII. In the combined cases of Ward and Sackett,⁸ Scheffey,⁹ and in this series, the salvage among the stump cancers was approximately twice that achieved with general carcinoma of the cervix in the same clinics. Healy and Arneson attribute their lower salvage rate to inadequate irradiation. They observe, however, that results were as good in patients whose lesions were advanced as with tumors of the same stage when the uterus was present. Their dosage for stump cancers was considerably lower than that used in the first four clinics in the table.

DISCUSSION

Distinctions are invariably made between the behavior of carcinoma of the cervix when the fundus is present and the same disease when the body of the uterus has been removed. "Stump cancer" is alleged

TABLE VIII. ELAPSED TIME BETWEEN HYSTERECTOMY AND RECOGNITION

YEARS	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Less than 3	2†	27	3	32
3-10	5	5	3	13
10 plus	7	12	3	22
Total	14	44	9	67

Poor salvage under three years. Fair salvage over ten years. Best salvage three to ten years.

*Alive, less than five years after treatment.

†Diagnosed by biopsy at time of hysterectomy.

In only 22 patients (33 per cent) was the disease recognized within six months of the appearance of the first symptom (Table IX). Eight of these (40 per cent) survived for five or more years, whereas the salvage among those treated one year or more after the first symptom was only 4.5 per cent.

TABLE IX. DURATION OF SYMPTOMS BEFORE RECOGNITION

TIME	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Less than 6 months	8	12	2	22
6-12 months	4	6	2	12
1 year or more	1	21	5	27
Not stated	1	5	0	6
Total	14	44	9	67

Best results secured when treatment was given early.

*Living, less than five years after treatment.

It has been pointed out^{6,7} that vesicovaginal fistulas are more common complications of carcinoma of the cervix when the fundus of the uterus has been removed. Their relatively frequent occurrence under these circumstances has been attributed to the destructive effects of the radium radiations to the bladder, mobilized into closer relationship with the stump of the cervix during hysterectomy. There were nine vesicovaginal fistulas in our combined series, an incidence of 13 per cent. In the group of cases from Philadelphia General Hospital, there were 6 vesicovaginal fistulas; an incidence of 25 per cent. Two of these patients also had rectovaginal fistulas. There were no fistulas in any of the patients who survived the five-year limit. Two of the 9 fistulas occurred in women who received no treatment at all. One of the patients was given only high voltage roentgen therapy. It would seem highly probable, therefore, that, as in carcinoma of the cervix in general, fistulas are due to the invasion of the cancer in cervical carcinoma after supravaginal hysterectomy rather than to the effects of the treatment. Table X shows the fistulas discovered among 1,117 carcinoma of the cervix patients from

TABLE X. FISTULAS OCCURRING IN 1,117 CASES OF CARCINOMA OF THE CERVIX, INCLUDING STUMP CARCINOMAS. GREATEST INCIDENCE WAS IN LATTER GROUP. UNTREATED CASES RANKED SECOND. (PHILADELPHIA GENERAL HOSPITAL.)

FISTULAS	NO. TREATED	NO. UNTREATED	NO. "STUMP CARCINOMAS"
	869	248	24
Vesicovaginal	34	49	4
Rectovaginal	39	0	2
Vesicovaginal and Recto- vaginal	13	16	2
Total	86 (10%)	65 (26%)	8 (33%)

the same clinic. Fistulas occurred three times as often in the untreated and "stump" cases as in the large group of treated patients with the fundus present.

Our findings are in accord with the opinion of Phaneuf that vesicovaginal fistulas are more frequently seen in carcinoma of the cervix when the fundus of the uterus has been removed than when it is retained. We submit, however, that this should not be attributed entirely to the effects of radiation but must in many instances be blamed on persistent invasion of the vesicovaginal septum by the carcinoma, in spite of the treatment administered.

SUMMARY

1. Carcinoma of the cervix after supravaginal hysterectomy behaves similarly to the same disease when the fundus is retained.
2. Its response to treatment is no worse than that of "cervix" cancer in general, and in some clinics is better.
3. Approximately 40 per cent of "stump" cancers recognized three years after subtotal hysterectomy, or within six months of the appearance of the first symptoms, were living and well five years after treatment.
4. Subtotal hysterectomy appears to improve the chance of cure if performed before carcinoma of the cervix has been acquired.
5. The probable development of vesicovaginal fistulas is greater than when the fundus is present. Fistulas are more often due to the disease than the result of treatment.
6. Meticulous examination of the cervix should be made a part of every gynecologic examination. Areas which are abnormal should be removed for histologic study. These principles are no less important when removal of the fundus is contemplated.
7. Complete hysterectomy is an excellent manner of dealing with disease of the cervix when the fundus is to be removed. However, in the hands of those whose experience is limited, supravaginal hysterectomy, combined with trachelectomy, is satisfactory and less hazardous.

REFERENCES

- (1) *Von Graef, E.*: AM. J. OBST. & GYNEC. 28: 18, 1934. (2) *Nuttall, J. E., and Todd, T. F.*: J. Obst. & Gynaec. Brit. Emp. 42: 860, 1935. (3) *Hunter, O. B.*: South. M. J. 32: 179, 1938. (4) *Stevenson, Charles S., and Scipiadès, Elmer, Jr.*: Surg. Gynec. Obst. 66: 822, 1938. (5) *Healy, W. P., and Arneson, A. N.*: AM. J. OBST. & GYNEC. 29: 370, 1935. (6) *Phaneuf, L. E.*: Am. J. Surg. 29: 479, 1935. (7) *Morton, D. G.*: Surg. Gynec. Obst. (Int. Abst. Surg.) 65: 177, 1937. (8) *Ward, George Gray, and Sackett, Nelson B.*: J. A. M. A. 110: 323, 1938. (9) *Scheffey, Lewis C.*: J. A. M. A. 107: 837, 1936. (10) *Meigs, J. V.*: AM. J. OBST. & GYNEC. 31: 358, 1936. (11) *Bartlett, M. K., and Smith, Geo. Van S.*: Surg. Gynec. Obst. 52: 249, 1931. (12) *Tagliaferro, P.*: Ann. di ostet. e ginec. 57: 1089, 1935.

3722 CHESTNUT STREET

DISCUSSION

DR LOUIS E. PHANEUF, Boston, Mass.—I have recently investigated 15,000 personal case histories and found stump carcinoma eight times, or once in 1,875 cases. In all instances, the supravaginal hysterectomy had been performed by other surgeons.

Eight patients were treated with radium, the largest dose being 6,100 mg. hr., and the smallest 2,400 mg. hr. In addition, 7 of the patients had high voltage x-ray therapy.

to be more refractory to treatment.^{5, 12} This has been attributed to difficulty in making proper application of radium in sufficient dosage when the uterine canal has been shortened by hysterectomy. Interference with circulation to the cervix due to contraction of scar tissue in the parametria, following the trauma of supravaginal hysterectomy, has been said to diminish the chance for curing the tumor of the stump.

In the course of our routine follow-up observations at the University and Philadelphia General Hospitals, we secured the impression that carcinoma of the cervix varied little in its characteristics whether or not the fundus was present when the disease was discovered. The data presented above show nothing peculiar about "stump" carcinoma with regard to age, initial symptoms, or histologic characteristics, as compared with carcinoma of cervixes from which the fundus has not been removed.

Our results as well as those from several other clinics indicate that the disease is just as amenable to treatment as when the fundus is present. In some instances, the results are distinctly better in "stump" carcinoma. It would seem logical to expect that after subtotal hysterectomy contractures of fibrous tissue in the parametrial regions might tend to keep the disease localized to the cervix for a relatively longer period of time. By compressing the blood vessels and lymphatics in these areas, the diminished circulation to the tumor might result in slower growth, and interference with lymphatic drainage should retard permeations. Castration, a procedure often performed with hysterectomy, has been recommended as a factor retarding the growth of carcinoma in other situations. There is no evidence to the contrary as far as carcinoma of the cervix is concerned. It is usually observed, furthermore, that carcinoma of the cervix is more rapidly invasive in patients of the younger age groups. The senilizing effects of castration should, therefore, be a favorable influence upon the course of the disease.

Before high voltage roentgen irradiations were available, it required considerable ingenuity to subject the carcinoma, situated in a short stump of the cervix, to cross-fire from the positions necessary to attain adequate dosage. This difficulty was overcome in many of the cases in our series by splitting the cervix transversely with a cautery to a depth equal to about one-half of the length of the stump. The radium tube was then placed crosswise within the lips of the split cervix. By augmenting the radium application with external irradiations, most of these tumors can be safely and adequately irradiated. Per-vaginal high voltage x-ray therapy was employed in one of our recent cases, as well as for more than 50 patients with ordinary cervical cancer. This form of irradiation seems peculiarly adapted for safe and thorough irradiation of cancerous cervixes after the fundus has been removed.

From the results secured in those "stump" cancers recognized three years after subtotal hysterectomy, it is perhaps fair to infer that the cervical carcinoma patient had a better chance of cure if the uterus had been removed before the cancer was acquired. The disastrous outcome of our patients whose carcinoma was discovered less than three years after supravaginal hysterectomy would indicate that removal of the fundus, after the carcinoma has been established in the cervix, is of no benefit.

I feel very definitely that the complete operation, a panhysterectomy, is to be preferred whenever it is possible to do it without additional danger to the patient.

DR. WILLIAM C. DANFORTH, Evanston, Ill.—It seems to me that there is a very strong argument for a wider use of the total operation which after all is the most effective type of prophylaxis against cervical cancer. Possibly the recommendation of this generally may not be wise, but in the hands of competent operators, I venture to say that the difference in mortality is *nil*.

In my own group within the past five or six years, there have been about 500 cases in which total abdominal hysterectomy has been carried out, either vaginally or abdominally, and we have not had any difference in mortality at all.

DR. FRANK A. PEMBERTON, Boston, Mass.—Our results at the Free Hospital for Women are about the same as Dr. Behney's. We have had 40 stump carcinomas in 780 cases of cancer of the cervix, a 6 per cent incidence. It is also of note that 10 (25 per cent) of our group occurred in nulliparas. Hence the fact that a woman has not borne children is not an indication for leaving the cervix in when deciding on whether or not to do a complete or supravaginal hysterectomy. The condition of the cervix is what counts.

The five-year salvage in this group was 16 patients, 40 per cent, about the same as Dr. Behney and Dr. Ward reported. Our series of cancers of the cervical stump extends over the period from 1909 to 1933. We treated 274 cases of cancer of the cervix between 1929 and 1933, inclusive, and have a five-year salvage of 38 per cent, about the same as for the salvage of stump cancer over the whole period.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Four years ago, at the Kansas City meeting of the A. M. A., I presented a similar study, a part of which I have brought up to date for this meeting, and offer as a contribution to this problem.

Table I shows the incidence of carcinoma of the cervical stump as seen on the Gynecologic Service at Jefferson Medical College Hospital from 1921 to 1940. The figure of 4.8 per cent approximates Dr. Behney's University of Pennsylvania figure. Of the entire series now presented, only one could be classified as a Group I (Schmitz) lesion. Fourteen were in Group III, 1 in Group IV, and 2 in Group V. Only 2 were adenocarcinomas and neither patient lived for very long. The youngest patient was 30; the eldest 72. About one-fourth (27.7 per cent) were under 40.

Table II depicts the comparative salvage (relative) between cervical carcinoma and cervical stump carcinoma. In our previous study, we reported a salvage of 42.8 per cent; today the figure is 41.6 per cent, a far better figure than we obtained in the treatment of carcinoma of the cervix in general. This is in accord with Dr. Behney's findings. The treatment has been predominantly with radium, and with a relatively high dosage, 3,000 to 4,500 mg. hr., with additional x-ray therapy in only a few instances.

Table III shows the salvage in relation to the lapse of time after the supravaginal hysterectomy. Since all of the patients successfully salvaged, with one ex-

TABLE I. INCIDENCE OF CARCINOMA OF CERVICAL STUMP

Carcinoma of cervix	369 patients
Carcinoma of cervical stump	18 patients
Incidence	4.8 per cent

TABLE II. COMPARATIVE FIVE-YEAR SALVAGE (RELATIVE) 1921 TO 1935

5-YEAR SALVAGE	CARCINOMA CERVIX PATIENTS TREATED—259	CARCINOMA CERVICAL STUMP PATIENTS TREATED—12
Including cancer death	23.5% (61 patients)	58.3% (7 patients)
Excluding cancer deaths	17.7% (46 patients)	
Present-day Salvage	15.8% (41 patients alive 5 to 19 years)	41.6% (5 patients alive 6 to 12 years)

In three women, the carcinoma existed in the cervix at the time of the subtotal hysterectomy. One is alive and well eleven and one-half years after the initial treatment, while the other two died two and one-fourth years and five months, respectively, afterward.

In the 5 remaining patients, the carcinoma developed in periods ranging from a short time to thirty years after the supracervical hysterectomy. Two are now alive and free from recurrence, five years and three months, and three years and five months, respectively, after treatment. Three have died, surviving the initial treatment three years and eleven months, one year, and seven months, respectively.

From the standpoint of prophylaxis, all these cases had had an indication for hysterectomy, and the total operation would have prevented the malignant lesion. This may serve as an argument in favor of the more common employment of panhysterectomy for benign lesions of the uterus.

DR. GEORGE GRAY WARD, New York, N. Y.—The last report from the Woman's Hospital on carcinoma of the stump was given about three years ago when Dr. Sackett reported an incidence of 7.2 per cent of carcinoma of the cervix after supravaginal hysterectomy. This report included all cases even though they occurred within the first year following the hysterectomy. I have recently had the records gone over from May, 1919, to May, 1940, and tabulated as follows:

Table I shows the survival rate. In 852 cases of cervical carcinoma seen during that period, 57 were stump cases, or 6.7 per cent. In 49 observed during a five-year period, 21 were living, or an absolute survival rate of 42.8 per cent. In 20 observed during a ten-year period, 10 were living, or an absolute survival rate of 50 per cent. One case of the 57 was not treated.

Table II shows the number of complications after irradiation. Three patients developed rectovaginal fistula, and 2 vesicovaginal fistula. With 5 in all the incidence of fistula was one and one-half times as high in stump cases as in the usual cervical cancers. The average duration of life in recurrent cases following treatment was fifteen months. Two patients died after two and three years from other diseases than carcinoma.

Table III shows the time between hysterectomy and postoperative radiation. Of the 57 cases, 16 developed within the first year after the hysterectomy. Of these first-year cases, 5 survived five years and 3 survived ten years. Undoubtedly in some of these patients the disease was present at the time of the hysterectomy. In 41 the disease developed more than one year after operation. Of these 16 survived five years, or 32.7 per cent of 49 observed, and 7 survived ten years, or 35 per cent of 20 observed. There were 28 cases arising three years following operation, or 3.28 per cent, which Dr. Behney mentioned as a better time limit to be sure that carcinoma was not present at the time of the hysterectomy.

Table IV gives both the Schmitz and the League of Nations classification of the extent of the carcinoma. In the 57 cases seen, 13 could be classified as early and 44 as advanced. Of the 13 patients with early cases 8 survived five years and 4, ten years. Of the 44 late cases, 13 patients survived five years and 6 ten years.

Table V shows that 45 cases were squamous cell, of which 20 survived five years, or 44 per cent, and 9 survived ten years, or 20 per cent. There were 10 cases of adenocarcinoma, 2 surviving five years, or 20 per cent, and 1 ten years, or 10 per cent. In 2 cases the type of cell was undefined.

Table VI shows the average dose of radium applied which was about 3,200 mg. hr. of element. High voltage x-ray follows or precedes, preferably given according to the Coutard technique. Before 1930 we had no high voltage x-ray. Thirty-six patients were treated with radium alone of which 29 were under treatment before 1930. Sixteen of these survived five years, and 9 survived ten years. Twenty patients were treated with both radium and x-ray, of which 5 survived five years, and 1 survived ten years. One patient was not treated.

I am in agreement with Dr. Behney in what he says about the behavior of these cases being in general similar to those in which there has been no hysterectomy. On the other hand, I believe that there is definitely more danger of fistula, owing to the proximity of the bladder.

TABLE I. CARCINOMA OF THE CERVICAL STUMP
COLLECTED STATISTICS

AUTHOR	NO. OF HYSTER- ECTOMIES	INCIDENCE STUMP CARCINOMA	AUTHOR	NO. OF HYSTER- ECTOMIES	INCIDENCE STUMP CARCINOMA
Lincoln		6.5%	Von Graef	4,269	0.62%
Lahey	900	2.0%	Hennington	18,712	0.57%
Sejourinet	5,712	1.9%	Albrecht		0.40%
White		1.8%	Fahndrich		0.40%
Richardson		1.0%	Meigs		0.13%
Scheffey	554	0.9%			

per cent. Dr. Phaneuf has just cited 15,000 cases of supravaginal hysterectomy with 7 instances of stump carcinoma following. The experiences of Ward, Scheffey, and ourselves indicate the curability of stump cancer to be about 40 per cent. It would seem, therefore, that the danger to the life of the patient from permitting the stump of the cervix to remain after hysterectomy is quite small.

In our own practice we perform total hysterectomy whenever the cervix is diseased, provided that there are no technical difficulties connected with this procedure which might increase the operative risk. Our policy in this regard is very little influenced by our fear of the development of carcinoma in the retained stump. We prefer total hysterectomy in such cases, because the removal of a diseased cervix disposes of a focus of infection, reduces morbidity, and greatly enhances the patient's chances for future good health.

It should also be emphasized that total hysterectomy is not the final solution of the problem of carcinoma as a later complication. Sejourinet, Lahey, and others have cited cases in which carcinoma of the vault of the vagina followed total hysterectomy. In our series at Philadelphia General Hospital, there were three patients who had carcinoma of the vault of the vagina following total hysterectomy and were, therefore, not included in this series.

The cases presented in this study were of patients operated upon by surgeons in the Philadelphia district. Some of them were by experienced gynecologists, a few by members of this Society. Yet there were a number of instances where carcinoma of the stump occurred within a comparatively short time after the supravaginal hysterectomy, and we are obliged to conclude that even experienced gynecologists at times perform supravaginal hysterectomy without careful study of the cervix. This occurs most frequently in instances where large tumors dominate the picture, and apparently insignificant disease of the cervix is disregarded. So long as this occurs, and so long as general surgeons, who do not enjoy the opportunity of a great gynecologic experience, must perform the gynecologic surgery in small hospitals, it seems entirely proper to recommend to those who consider themselves incapable of performing total hysterectomy, the alternative of supravaginal hysterectomy with amputation of the cervix and careful study of the removed tissues.

ception, showed relatively advanced lesions, it would seem that carcinoma of the cervical stump has been remarkably amenable to radiation therapy, irrespective of the lapse of time after supravaginal hysterectomy.

TABLE III. SALVAGE IN RELATION TO LAPSE OF TIME AFTER SUPRAVAGINAL HYSTERECTOMY

YEARS AFTER	NUMBER PATIENTS	5-YEAR SALVAGE (CANCER DEATHS)	PRESENT-DAY SALVAGE
1 to 3	5	0	2 (8, 12 yr.)
3 to 10	6	2 (6, 9 yr.)	1 (12 yr.)
10 to 25	7	0	5 (½, 1, 3, 6, 10 yr.)

DR. LILIAN K. P. FARRAR, New York, N. Y.—Why comfort oneself with the thought that a carcinoma of the cervix can be treated just as well after the fundus is taken out? Take out that cervix with the fundus and the patient will not have the carcinoma.

Dr. Pemberton demonstrated last year the pathologic condition of the cervix in a series of total hysterectomies. Dr. Danforth has told you that the same mortality is possible after a total as after a supravaginal hysterectomy. Yet we continue to say that total hysterectomy should not be generally advised and that it is not for the average surgeon. I earnestly urge this Society not to be satisfied with merely devising methods for the inadequately trained surgeon, but to raise the standards of pelvic surgery and give better protection to American women.

DR. JAMES C. MASSON, Rochester, Minn.—In the Mayo Clinic, at the last compilation, we had found 164 and, I am sure by now, there are 170 cases of carcinoma in the cervical stump. We also have seen about 500 patients who had cervicitis with leucorrhea which was sufficient to require treatment. In many of these cases there was no history of leucorrhea before the body of the uterus had been removed.

I agree with what Dr. Farrar has said. Why should the members of this Society, who specialize in gynecology, advise subtotal operation as often as they do? If the complete operation can be done as safely as the subtotal, and I believe it can, why should we do so often the subtotal operation?

DR. WILLIAM A. SCOTT, Toronto, Canada.—Although it is my belief that total hysterectomy should play a larger part in the operative procedure of the skilled gynecologist, I would like to point out a fallacy in the present argument. It is stated that cases in which carcinoma of the stump develops within three or five years should be looked upon as having been present at the time of operation. Nevertheless, in Dr. Farrar's paper last year, there were 460 cases of total hysterectomy for benign conditions, and in none of these was an unsuspected carcinoma discovered after careful pathologic examination of the cervix. In the discussion of that paper, I noted only one instance in my series where such unsuspected carcinoma was found, and Dr. Pemberton found no example in 100 consecutive cases on whom he had operated. It would appear, therefore, that in these series at least, unsuspected cancer at the time of operation was of no significance, and had subtotal hysterectomy been done, subsequent cancer of the stump, had it developed, would have been a new disease.

DR. HERMANN J. BOLDT, White Plains, N. Y.—I have had a fairly large experience of something over fifty years and in my opinion the important thing to remember is to see what the condition of the cervix is at the time of operation. Invariably a complete hysterectomy should be done if an eroded cervix exists.

DR. BEHNEY (closing).—I should like to clarify my attitude toward total and subtotal hysterectomy. Statistics (Table I) show an incidence of carcinoma of the stump varying from 0.1 to 6 per cent of the subtotal hysterectomies performed. The number of cases considered is not stated in all instances, but Sejourinet has reported over 5,000 hysterectomies with 1.9 per cent of carcinoma of the cervix following, and in the large series reviewed by Hennington, the incidence was 0.57

age time waste from the first medical examination to the institution of treatment was approximately four months, a total time waste of approximately eleven months.

TABLE II. DURATION OF SYMPTOMS

DURATION OF SYMPTOMS	NUMBER	PER CENT
No symptoms	3	1.6
No delay, treatment sought immediately	3	1.6
Delay of one month or less	40	22.4
Delay of 2 to 3 months	16	8.7
Delay of 3 to 6 months	35	19.0
Delay of 6 to 12 months	30	16.3
Delay of 12 to 18 months	13	7.1
Delay of more than 18 months	43	23.5
Total	183	100.2

TABLE III. TIME WASTE PRIOR TO SEEKING ADVICE AND TREATMENT

AVERAGE TIME WASTE	MONTHS	WEEKS	DAYS
From onset of symptoms to diagnosis	7.1	28	196
From diagnosis to beginning of treatment	4.0	16	112
Total	11.1	44	308

TABLE IV. COMPARATIVE STUDY OF TIME WASTE AMONG PATIENTS WITH CORPUS CARCINOMA

REPORTED BY	AVERAGE TIME WASTE— ONSET OF SYMPTOMS TO DIAGNOSIS			AVERAGE TIME WASTE— DIAGNOSIS TO BEGINNING OF TREATMENT			TOTAL TIME WASTED
	DAYS	WEEKS	MONTHS	DAYS	WEEKS	MONTHS	MONTHS
Miller,* 1929	448	64.0	16.0	266	38.0	9.5	24.0
Collins,† 1934	250	35.6	8.9	103	14.7	3.8	12.7
Miller, 1940	196	28.0	7.1	112	16.0	4.0	11.1

*Reported (in 1933) from University of Iowa.

†From University of Iowa.

This represents a considerable improvement (see Table IV) when compared with a somewhat similar study made by me¹ in 1929 and by Collins² in 1934 at the University of Iowa. While the data in Table IV come from two widely separated clinics in two different states, it is fair to assume that the general trend toward earlier diagnosis and treatment is real.

Table V shows that *65 per cent of the patients are now undergoing treatment within three months* after seeking medical advice. Patients included in this series come

TABLE V.* TIME WASTE BETWEEN FIRST MEDICAL EXAMINATION AND INSTITUTION OF TREATMENT

One month	70 patients or 48.0%	} 65%
Two months	16 patients or 10.0%	
Three months	11 patients or 7.0%	
Four months	3 patients	
Five months	1 patient	
Six months	5 patients	
Seven months	5 patients	
Eight months	1 patient	
Nine months	3 patients	
Ten months	1 patient	
Eleven months	2 patients	
Twelve months	9 patients	
Delay of more than one year	20 patients	

*In calculating the percentages, all patients delaying more than one year before the institution of treatment were omitted in order to avoid excessive distortion.

CARCINOMA OF THE BODY OF THE UTERUS*

NORMAN F. MILLER, B.S., M.D., F.A.C.S., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

THE complacency which characterizes treatment of corpus carcinoma probably has a twofold origin, (1) the fallacious belief that the prognosis is invariably good, and (2) the tendency to compare results with other less amenable carcinomas. Survival studies have shown that the prognosis is not always good, and further that we have not yet taken full advantage of the remedial measures at our command.

This study is based on 183 patients with microscopically verified carcinoma of the body of the uterus seen in the Gynecological Tumor Conference at the University of Michigan Hospital since April, 1931. It also includes 3 patients seen in 1930. All patients have been followed since their original examination, there are no untraced cases. While we are primarily interested in the results of therapy considerable data of general interest have been tabulated.

GENERAL STATISTICS

Age.—The average age for the entire group was fifty-four years.

Race.—Among the 183 patients, only one was colored. The remainder were white.

Geographic Distribution.—All but 8 patients in our series came from the State of Michigan. They constitute a large number of the more advanced cases coming, as they do, from the poorer economic group.

Marital status.—One hundred and seventy-seven patients were married, six were single. Of the 183, 135 (73 per cent) had been pregnant, 48, or 27 per cent, had never conceived. The average number of children among the former was 3.1. Only 30 had 5 or more children.

Symptoms.—The chief symptoms noted were as indicated in Table I.

TABLE I. SYMPTOMS

SYMPTOM	NUMBER	PER CENT
No symptoms	3	1.6
Bleeding or spotting	160	88.0
Nonbloody discharge	8	4.3
Tumor mass	6	3.2
Pelvic pain	6	3.2
Total	183	100.3

Duration of Symptoms.—The duration of symptoms is an indication of time wasted, chiefly by the patient. Information on this point is presented in Table II.

Since time wasted by patients prior to seeking advice is of tremendous importance, further comment regarding this observation is desirable. Among 147 patients with abnormal bleeding, there existed an average time waste of 7.1 months prior to the patient's seeking advice concerning the cause of the bleeding. The aver-

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Que., June 17 to 19, 1940.

TABLE VII

	MILLER		SCHEFFY AND THUDUM	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Low	101	64.7	22	32.3
Intermediate	50	32.0	27	39.7
High	5	3.2	18	26.4
		99.9		98.4

While our series reveals a high incidence of so-called lower grades and few highly malignant cases, I am satisfied that this is a matter of interpretation rather than due to any climatic or geographic factor which renders corpus carcinoma less malignant in Michigan.

The relationship between histologic grade and survival has been pointed out by others^{7, 9} and is further born out by this study. Among the 68 eligible for five-year survival, the relationship between grade and survival is shown in Table VIII.

TABLE VIII. RELATION BETWEEN HISTOLOGIC GRADE AND SURVIVAL

HISTOLOGIC GRADE	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER SURVIVORS	PER CENT OF SURVIVORS FOR EACH GRADE	NUMBER DEAD
1	17	25	13	76	4
2	30	44	17	57	13
3	18	26	7	39	11
4	3	4	1	25	2
	68	99			

Clinical Classification.—Several clinical classifications have been attempted. Crossen's⁵ clinical grouping is based on findings at the time of operation. Healy and Brown⁶ base their classification on palpable size of the uterus and believe that a small or normal-sized uterus is associated with a better prognosis. All of our cases were carefully examined and, as an additional check on size, the length of the uterine cavity was measured. While this procedure was helpful, we do not necessarily advocate it as a routine procedure. On the basis of palpable size and length of uterine cavity, we were able to divide our patients into three groups, thus: Group I, normal size, revealing no palpable enlargement of the uterus and a uterine cavity measuring 3 inches or less; Group II, the moderately enlarged, including those with enlargement of the uterus up to size of a two and one-half months' pregnancy and a cavity measuring not more than 4½ inches; Group III, markedly enlarged, including all patients with a uterus larger than a three months' pregnancy, and a cavity measuring more than 5 inches.

TABLE IX. CLINICAL GROUPING ACCORDING TO UTERINE SIZE AMONG ALL 68 PATIENTS ELIGIBLE FOR PERCENTAGE FIVE-YEAR SURVIVAL (UNCORRECTED)

	NO. OF PATIENTS	PER CENT OF TOTAL	LIVING	PER CENT OF GROUP LIVING	DEAD
Group I (Normal). No palpable enlargement of uterus. Cavity measures 3 inches or less.	21	31	14	66	7
Group II (Moderately enlarged). Enlarged uterus up to 2½ mo. pregnancy. Cavity measures less than 4½ inches.	34	50	19	56	15
Group III (Markedly enlarged). Uterus size 3 mo. pregnancy or more. Cavity measures more than 5 inches.	13	19	3	23	10
	68	100	36		32

largely from the lower economic rank, and this three-month delay is partly explainable on the basis of time required for filter board examinations and for making home, transportation, and hospitalization arrangements.

While the average age in this series was 54 years, the lesion often occurs in younger women. Among the 183 patients studied, 142, or 77 per cent, were fifty years of age or over. Forty-one, or 22 per cent, were forty-nine years of age or under. While this age division is arbitrary and does not necessarily draw the line between the pre- and the postmenopausal groups, it may be assumed that the majority fifty years or over were past the menopause, and similarly, many forty-nine years of age or under were still menstruating. This assumption is justified on the basis of the report by Crossen and Hobbs³ on the relationship of late menstruation to carcinoma of the corpus.

Since so much importance has been attached to bleeding late in life, it was of interest to determine how many of these women had a curettage as part of their original diagnostic study. Curettage was done in only 40, or 28 per cent, of the women over fifty. In other words, 72 per cent with significant bleeding occurring after the fiftieth year of life did not have what is considered an important diagnostic procedure as a means of determining the cause of the symptom. Twenty-six, or 65 per cent, of the women forty-nine or under had no curettage as part of their original diagnostic study. While neglect is not necessarily indicated by failure to perform a curettage, it appears that the value of this procedure is not yet fully appreciated. Unquestionably many physicians felt that curettage was indicated but chose to refer the patient directly to a specialist for both diagnosis and treatment.

Fibroids Associated With Corpus Carcinoma.—Thirty-one, or 19.8 per cent, of 156 patients treated entirely by us had fibroids. Twelve, or 40 per cent, of these 31 patients are dead. Morton believes the outlook somewhat poorer in patients with fibroids, but we are not impressed with the fact that they particularly affect the prognosis.

Double Primary Carcinoma.—Five of our patients had more than one primary carcinoma. The combinations noted were breast 1, cecum 1, sarcoma in uterine fibroid 1, lymphoblastoma 1, and rectum 1. Three of these patients are dead, the two with rectal and cecal primaries are still living after appropriate treatment directed toward both uterine and intestinal lesions.

Metaplasia.—Definite metaplasia, sometimes marked with extensive areas of squamous epithelium in the uterine carcinoma, was noted in 15 per cent, or 23 times. The significance of this change is not entirely clear nor does it appear to affect the prognosis (16 living, 7 dead). Meigs¹⁰ and Schattenberg and Ziskind¹¹ consider the prognosis somewhat poorer in adenoacanthoma, but we did not observe any such influence in our cases.

Histologic Classification of Tissues.—One hundred and fifty-six patients were treated entirely by us. The remaining 27 were treated in part elsewhere and were not included in the remainder of this analysis.

Tissues not originally classified were re-examined and graded by me. The basic criteria for grouping were generally similar to those commonly used.

TABLE VI. HISTOLOGIC GRADING IN 156 CASES OF CORPUS CARCINOMA TREATED BY US

	NO. CASES	PER CENT
Grade I	23	14.7
Grade II	78	50.0
Grade III	50	32.0
Grade IV	5	3.2
	156	99.9

Since a single section may reveal several grades of malignancy, it is natural that in grading there shall exist some difference of opinion. This emphasizes the desirability of broad grouping such as used by Scheffey and Thudium⁴ (low, intermediate, high). Classification on this simplified basis is shown in Table VII.

uterus does not necessarily imply a superficial localized neoplasm, further evidence that such precautionary measures as preoperative radiation and minimal operative manipulation are desirable for successful therapy.

TABLE XII. CORRELATION BETWEEN SIZE OF UTERUS AND EXTENT OF LESION AMONG ALL 85 HYSTERECTOMIZED PATIENTS (CORRECTED FOR NONCARCINOMA DEATHS)

SIZE OF UTERUS	EXTENT OF LESION			TOTALS FOR SIZE OF UTERUS
	1	2	3	
1	1 dead 17 living or 94%	0 dead 4 living or 100%	2 dead 9 living or 81%	3 dead 30 living or 90%
2	1 dead 20 living or 95%	0 dead 10 living or 100%	3 dead 7 living or 70%	4 dead 37 living or 90%
3	0 dead 1 living or 100%	4 dead 1 living or 20%	1 dead 4 living or 80%	5 dead 6 living or 54%
Totals for extent of lesion	2 dead 38 living or 95%	4 dead 15 living or 78%	6 dead 20 living or 76%	

TREATMENT

Cure may be achieved by (a) removal or (b) destruction of the lesion in situ. For far-advanced cases and for those unable to withstand operation, irradiation is obviously the treatment of choice. The difficulty of adequately irradiating the uterine cavity is well known. The problem has not been solved by multiple applicators, multiple applications nor ingenious devices.

In very early lesions surgery alone may be satisfactory. For most patients, however, both irradiation and surgery are indicated. It is a mistake to look upon irradiation and surgical extirpation as competitive measures. Both have a place in treatment and both have proved their usefulness.⁷ In general, best results should be achieved by using both surgery and irradiation, one supplementing the other.

During the period covered by this study, the usual forms of treatment were utilized. When possible, however, operation was preceded by irradiation (75 cases). We believe the evidence presented in this and other reports clearly indicates the desirability of utilizing both radiation and surgery, one supplementing the other. We prefer preoperative x-ray followed by total hysterectomy, six weeks after completion of the x-ray.

Preoperative irradiation reduces the hazard of dangerous spill and manipulative spread at the time of operation and also makes the operation easier by reducing congestion if carried out at the optimum time (six weeks following completion of irradiation). When reliance must be placed on irradiation alone, as in poor physical risks, x-radiation should be followed by an intracavitary radium application. The effect of radium upon endometrial carcinoma has been described by Arneson⁸ as characterized by the breaking up of the glandular structure, swelling, pyknotic fragmentation of nuclei, necrosis, leucocytic infiltration, and slough. Similar changes may be noted following x-radiation. Indeed,

The findings presented in Table IX confirm the general opinion as well as that expressed by Healy and Brown⁶ that corpus carcinoma found in a small or normal-sized uterus is generally associated with a better prognosis. That this is not always true, however, is proved by patients with moderate or even marked enlargement of the uterus who recover. Tables X, XI, XII, and XIII bear further on this aspect of the problem. It will be noted that these factors are generally significant only and are not infallible indicators of prognosis.

Extent of Lesion as Noted in Gross Specimen Removed at Operation.—Eighty-five of the 156 patients treated by us were operated upon and the specimens subjected to gross and microscopic study. The findings permitted classification into three groups as shown in Table X. However it must be noted that all but 10 of the 85 patients operated upon received preoperative irradiation, and consequently a much different grouping might have been noted had there been no such preoperative irradiation.

TABLE X. EXTENT OF LESION BASED ON MICROSCOPIC AND GROSS EXAMINATION OF SPECIMEN REMOVED AT TIME OF OPERATION (HYSTERECTOMY, BILATERAL SALPINGO-OOPHORECTOMY). IN 85 CASES

GROUP	NO. EACH GROUP	PER CENT
Group I. (No carcinoma found or local and/or superficial growth. No deep infiltration.)	40	47.0
Group II. (More extensive than I and less than III. Not more than halfway through uterine wall.)	19	22.3
Group III. (Widespread and/or deep infiltration through more than one-half uterine wall.)	26	30.0
	85	99.3

Thirty-nine of the 85 patients operated upon were eligible for five-year survival. Five were treated by operation only and the remaining 34 by some form of preoperative radiation followed by operation. Among these 39 cases, the extent of the gross lesion is revealed in Table XI.

TABLE XI. EXTENT OF NEOPLASTIC INVOLVEMENT IN THE 39 PATIENTS OPERATED UPON MORE THAN FIVE YEARS AGO AND THEREFORE ELIGIBLE FOR FIVE-YEAR SURVIVAL

GROUP	NO.	LIVING	PER CENT LIVING IN EACH GROUP	DEAD
Group I. (No carcinoma found or superficial, local.)	18	15	83.0	3
Group II. Moderately widespread. (Moderate invasion but not beyond one-half uterine wall.)	8	6	75.0	2
Group III. Widespread. Extensive. Deeply infiltrating. (More than one-half thickness of uterine wall.)	13	8	61.5	5

As expected, we noted a higher incidence of five-year survivors in Group I, but 61 per cent of Group III cases also survived five years or more. This is significant and should influence our attitude regarding therapy. Because the lesion is widespread and deeply invades the uterine wall does not necessarily mean a poor prognosis. In advanced cases, it would appear desirable that tumor cells be rendered inactive and operative manipulation be reduced to a minimum. By so doing the hazard of spill and manipulative spread should be decreased.

Correlation between uterine size and extent of the lesion was attempted in Tables XII and XIII. It will be noted that a large, easily palpated uterus does not always mean deep infiltration of the uterine wall. Likewise a normal-sized

Much emphasis has been placed on the use of intracavitary radium, and we believe this desirable where dependence must be placed on irradiation alone or when the patient is too obese for adequate external x-radiation. When, however, surgical extirpation is planned, our preference is for preliminary x-radiation because of: (a) its detrimental effect upon the tumor cells, (b) its known effectiveness in reducing congestion, (c) ease of application, (d) absence of uterine manipulation, and (e) no necessity for anesthesia or operating room setup.

Results of treatment in this study are shown in Tables XIV and XV.

TABLE XIV. TYPE OF TREATMENT USED IN 156 CASES OF CORPUS CARCINOMA

TYPE OF TREATMENT		NO. TREATED
Radiation:		
Radium	22	
X-ray	9	
Radium and x-ray	40	71
Operation		10
Radiation + Operation		75
Total		156

TABLE XV. RESULTS OF TREATMENT AMONG 68 PATIENTS ELIGIBLE FOR FIVE-YEAR SURVIVAL

	NO. OF CASES	PER CENT OF TOTAL	LIVING	PER CENT OF GROUP LIVING	DEAD
Irradiation	29	42.6	10	34.4 (Corrected 37%)	19
Operation	5	7.3	4	80.0 (Corrected 100%)	1
Irradiation + Operation	34	50.0	24	70.5 (Corrected 82.3%)	10

Naturally patients too far advanced to be operated upon are included among those treated by irradiation. Yet, only seven of the 29 so treated by us fell into this classification. In the remaining 22, the reason was some physical factor preventing operation or else a flat refusal on the part of the patient (2 cases). By removing the 7 advanced cases, we find among the 22 patients treated by irradiation only 7 living and 15 dead or a five-year survival rate of 32.4 per cent as compared with 70.5 per cent (corrected 82.3 per cent) for combined irradiation and operation. Two, or 6.8 per cent, of the irradiated group have since died of carcinoma, whereas no such late carcinoma deaths have occurred among the operated or combined irradiated and operated groups. The five patients treated by operation only reveal 4 five-year survivors, too small a number to permit comment.

One patient hopelessly advanced was not treated. If this case be included in our group eligible for five-year survival, we find an absolute survival rate (five years) from all methods of treatment of 52.1 per cent.

preoperative radiation may result in complete destruction of the neoplasm. This has been noted by many observers. We are impressed by such evidence of the effectiveness of radiation. Many patients who ultimately die from carcinoma following hysterectomy alone possibly do so because of unavoidable manipulative spread at the time of surgery. Because of its proved effectiveness, preoperative irradiation should reduce this hazard. Our observations have convinced us that surgical extirpation six weeks following completion of preoperative radiation is today the most desirable form of treatment for most corpus malignancies.

TABLE XIII. CORRELATION BETWEEN SIZE OF UTERUS AND EXTENT OF LESION AMONG 39 PATIENTS OPERATED UPON WHO WERE ELIGIBLE FOR FIVE-YEAR SURVIVAL (CORRECTED FOR NONCARCINOMA DEATHS)

SIZE OF UTERUS	EXTENT OF LESION			TOTALS FOR SIZE OF UTERUS
	1	2	3	
1	1 dead 7 living or 87%	0 dead 3 living or 100%	1 dead 3 living or 75%	2 dead 3 living or 86%
2	0 dead 9 living or 100%	0 dead 2 living or 100%	1 dead 5 living or 83%	1 dead 16 living or 93%
3	0 dead 1 living or 100%	3 dead 0 living or 0%	1 dead 2 living or 67%	4 dead 3 living or 42%
Totals for extent of lesion	1 dead 17 living or 94%	3 dead 5 living or 62%	3 dead 10 living or 76%	

While we are impressed with the effectiveness of radiation, we cannot overlook the fact that residual neoplastic tissue is often seen in the removed specimen. Preoperative irradiation may have destroyed much of the disease yet the frequency with which healthy-appearing carcinoma is found warrants the belief that irradiation alone, at least in its present mode of application, is not a thoroughly reliable remedy for corpus cancer. The absence of neoplasm in removed specimens following preoperative radiation may in some cases be more apparent than real. Unobserved localized cell nests may still be present which, if permitted to remain, will ultimately cause the patient's death. The fact that there exists a higher late death rate among the *operable* patients treated by irradiation only tends to emphasize this point.

Others have pointed out the correlation between histologic grade and survival rate. Our own observations have corroborated the serious outlook for patients with more highly undifferentiated types of carcinoma. Yet, we cannot subscribe to the view that histologic grade shall dictate choice of treatment. While tissue grading is helpful it is only one of several factors influencing prognosis. We are not impressed with the fact that early and intermediate grades of endometrial carcinoma are so much more radioresistant than the highly undifferentiated, a point which appears to have been emphasized by others. In our series, preoperative irradiation has destroyed all evidence of carcinoma as determined by study of the removed specimen in all histologic grades.

MORBIDITY

Morbidity in carcinoma patients is not easy to evaluate. In our series morbidity was high and much of it attributable to radiation. The proponents of surgery alone may here find a potent argument against combining the two forms of treatment. Because of the difficulty in determining primary cause, no attempt is made to discuss morbidity at this time. For distribution see Table XVII.

TABLE XVII. MORBIDITY NOTED IN 156 PATIENTS WITH CARCINOMA OF THE UTERINE BODY

I. Gastrointestinal:
Severe diarrhea
Intestinal obstruction
Rectal stricture
Fistula
Anorexia
II. Genitourinary:
Urethrocystitis, etc.
Stricture (ureteral)
Hydronephrosis
Fistula
Abscess (paranephritis)
Incontinence
III. Skin:
Wound infection
Severe dermatitis
Toxic erythema
Erysipelas
IV. Nervous system:
Pain, severe, necessitating:
Strong sedation, morphine
Alcohol injections
Chordotomy
V. Bones:
Metastasis
Fractured femur
VI. Respiratory:
Pneumonia
Pulmonary embolism
Lung metastases

SUMMARY AND CONCLUSIONS

1. The basis for this study was 183 cases of corpus carcinoma, of which 156 were treated entirely by us and 68 were eligible for five-year survival.

2. The average time waste from onset of symptoms to beginning of treatment was approximately eleven months. This is an improvement when compared with previous reports on time waste.

3. Sixty-five per cent of patients in this series had commenced treatment before the fourth month after onset of symptoms.

4. (a) Histologic grading of endometrial carcinoma is only one of several factors helpful in determining prognosis. (b) We are not impressed with the fact that histologic Grades I and II are particularly radioresistant.

Regardless of uterine size, histologic grade, or gross extent of the lesion we are able to report:

1. There were 34.4 per cent five-year survivals following irradiation treatment alone. Corrected for noncarcinoma deaths, this figure becomes 37 per cent. However, two in this group have since died of carcinoma.

2. There were 70.5 per cent five-year survivals following combined irradiation and operation. Corrected, this figure becomes 82.3 per cent. None of these five-year survivors have yet died of carcinoma.

Response of Grade IV Carcinoma to Treatment.—Only four of our 156 patients were considered to have true Grade IV carcinoma. One of these patients is living and well today seven years following treatment by preoperative x-ray and operation. The response to x-ray in this case appears to have been remarkable since the uterus revealed no carcinoma when studied following hysterectomy. Two patients were treated by x-ray, radium, and operation. One died within a year and the other, four years after treatment. The fourth patient refused operation and received x-ray only. She lived one year following treatment.

MORTALITY

We have definite information regarding 45 deaths in our series. Carcinoma was the chief cause in 71 per cent. Other causes are revealed in Table XVI.

TABLE XVI. CAUSE OF DEATH IN 45 PATIENTS WITH CARCINOMA OF THE UTERINE BODY

CAUSE	NUMBER IN GROUP TREATED BY IRRADIATION ONLY	NUMBER IN GROUP TREATED BY IRRADIATION + OPERATION	TOTAL	PER CENT
Carcinoma	23	9	32	71.1
Heart	3	3	6	13.3
Pneumonia	1	1	2	4.4
Embolism	1	1	2	4.4
Intestinal Obstruction	0	2	2	4.4
Carcinoma of Stomach	1	0	1	2.2
			45	99.8

OPERATIVE MORTALITY

There were three operative deaths among the 85 hysterectomized patients (10 hysterectomy only, 75 irradiation plus hysterectomy), an operative mortality of 3.5 per cent.

Cardiac failure, ninth postoperative day	1 case
Pneumonia, tenth postoperative day	1 case
Peritonitis and intestinal obstruction, fifth postoperative day	1 case
Total	3

All three deaths occurred in patients who had received no preliminary irradiation as part of their treatment. There was no immediate mortality following irradiation.

In these patients who have passed the menopause one should have radium available and ready to be placed in the uterus while awaiting the pathologist's report. I am very much against depending upon preliminary roentgen irradiation alone in these cases, even though one is planning a hysterectomy.

Histologic grading, as Dr. Miller says, is one of several factors in determining prognosis. It is a helpful factor and may be of importance in this way. If a patient has been curetted elsewhere and a diagnosis returned of adenocarcinoma of Grade I or II, we are justified in going forward with a hysterectomy immediately, without any preliminary roentgen or radium irradiation. That is the procedure which I follow. I think that hysterectomy in the operable cases will cure 90 per cent or more of those cases.

A uterus with a cancer of the corpus which does not exceed a two and one-half months' gestation in size is a very favorable case for cure by any method of procedure, provided it is a competent method such as a complete hysterectomy, either with or without irradiation, depending upon the histology of the case. In Group II I have placed all uteri larger than two and one-half months' gestation, and in Group III those patients with metastases.

I hope that you will all consider the clinical grading as well as the histologic grading of your cases in trying to make your prognoses. If you will do that there is no doubt that the end results will be improved; especially in cases where the uterus is not more than a two and one-half months' gestation in size. The hysterectomy should not be done too soon after irradiation. We usually wait about eight weeks.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—The analysis of Dr. Miller's material corresponds in general with our own experience on the Gynecologic Service at Jefferson Medical College Hospital. We, too, have no untraced patients. Four per cent of our patients were under 41 years; 24 per cent were under 50; 72 per cent were over 50. Only one of our group was a negress. Our nulliparous incidence is a bit higher than Dr. Miller's—27 per cent.

I am glad that Dr. Miller's present study shows an improvement in respect to the time wasted before treatment was instituted. A report made by us three years ago showed a situation very similar to his earlier findings, with the added interesting feature that the waste of time in patients with postmenopausal bleeding was nearly twice as great as that in patients with atypical premenopausal bleeding.

The frequent failure to perform or advise diagnostic curettage when urgently indicated has been proved by Dr. Miller's figures, and our records likewise emphasize this appalling neglect. At this point I wish to call attention to two factors which may either delay diagnosis or be responsible for the initiation of incorrect therapy. I refer, first of all, to ill-advised hormonal therapy, administered in the belief that the atypical bleeding is functional, and second, to the assumption that the presence of a myoma is the sole cause of atypical or postmenopausal bleeding. Myomas were associated with fundal carcinoma in 25 per cent of our series, a somewhat higher incidence than that reported by Dr. Miller.

At Jefferson we are in accord with Dr. Miller's premise that preoperative radiation is both desirable and essential. Generally we prefer preoperative radium to preoperative x-ray, but Dr. Miller has made out a good case for x-ray. We agree entirely that whenever the extent of the lesion and the condition of the patient permit, surgical extirpation should follow in six to eight weeks. The plan of treatment followed at Jefferson is as follows:

1. Diagnostic dilatation and curettage with radium available.
2. Rapid histologic report.
3. Preliminary radiation with radium.
4. Subsequent panhysterectomy or further radiation dependent upon individualization.

Dr. Miller's figures show the decided advantage in his hands of combined irradiation and operation, regardless of clinical or histologic classification. With the higher grade malignancies, we feel that preoperative radiation offers more than

5. Clinical grouping based on size of the uterus is practical. Our findings tend to bear out the general feeling that corpus carcinoma in a small or normal-sized uterus is associated with a somewhat better prognosis.

6. Methods of treatment and results are discussed and the following views expressed: (a) For inoperable cases of corpus carcinoma whether due to complicating illness or extent of disease, x-ray followed by intracavitary radium is the procedure of choice. By this method we obtained 34.4 per cent five-year survivors (37.0 per cent when corrected for noncarcinoma deaths). (b) For operable cases with possible exception of extremely early lesions, we advise preoperative irradiation followed by total hysterectomy six weeks after completion of the radiation treatment. (c) X-ray is preferred to intracavitary radium for preoperative irradiation whenever possible. (d) By combining preoperative irradiation with surgery, we are able to report 70.5 per cent five-year survivors (82.3 per cent when corrected for noncarcinoma deaths). (e) Radiation and surgery should not be looked upon as competitive forms of therapy but as remedial measures of proved value. Best results are obtained by using both in a supplementary manner.

7. Fibroids were found in 19.8 per cent of our cases. We cannot say that fibroids affect the prognosis.

8. Five patients had a double primary.

9. Metaplasia was common, occurring in 15 per cent. Its significance was not clear. It did not appear to affect prognosis.

10. Study of mortality revealed carcinoma as the cause of death in 71.1 per cent of 45 patients with complete data. Other causes included heart disease, pneumonia, embolism, intestinal obstruction, etc.

11. Primary operative mortality in 85 patients was 3.5 per cent (1 cardiac, 1 pneumonia, 1 peritonitis).

REFERENCES

- (1) Miller, Norman F.: J. Iowa M. Soc. 23: 132, 1933. (2) Collins, R. M.: Ibid. 24: 71, 1934. (3) Crossen, Robt. J., and Hobbs, John E.: J. Missouri M. A. 32: 361, 1935. (4) Scheffey, Lewis C., and Thudium, Wm. J.: AM. J. OBST. & GYNEC. 34: 1006, 1937. (5) Crossen, H. S.: Ibid. 33: 587, 1937. (6) Healy, Wm. P., and Brown, Robert L.: Ibid. 38: 1, 1939. (7) Healy, Wm. P., and Cutler, Max: Ibid. 19: 457, 1930. (8) Arneson, A. N.: Am. J. Roentgenol. 36: 461, 1936. (9) Morton, Daniel G.: Am. J. Roentgenol. 41: 789, 1939. (10) Meigs, J. V.: Tumors of the Female Pelvic Organs, New York, 1934, The Macmillan Co., p. 140. (11) Schattenberg, Herbert J., and Ziskind, Joseph: AM. J. OBST. & GYNEC. 39: 112, 1940.

DISCUSSION

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—If I understand Dr. Miller correctly he states that he much prefers preoperative roentgen irradiation to intrauterine radium irradiation. He is not discussing the treatment of cancer of the corpus uteri by roentgen ray alone, but merely the preparation of the surgical field for the hysterectomy which is to follow within six weeks. It must be thoroughly understood that he does not recommend roentgen therapy for the cure of cancer of the corpus uteri. For this purpose one must combine the roentgen therapy with intrauterine therapy.

I must disagree with one of the reasons which Dr. Miller gives for not using intrauterine preoperative irradiation with radium. He states that he avoids anesthesia and manipulation of the uterus. Yet after all we must make a diagnostic curettage and for this the patient usually is under an anesthetic.

PRIMARY CANCER OF THE FALLOPIAN TUBE*

A CONSIDERATION OF ITS INCIDENCE, CLINICAL DIAGNOSIS, AND TREATMENT, WITH THE REPORT OF A CASE DIAGNOSED BEFORE OPERATION

KARL H. MARTZLOFF, M.D., PORTLAND, ORE.

(From the Department of Surgery, University of Oregon Medical School)

FROM a purely clinical aspect, primary cancer of the Fallopian tube offers three points of major interest; namely, its apparent infrequency, the difficulty of its clinical diagnosis, and the unsatisfactory status of its treatment.

One cannot but be impressed by the observation that, while the Fallopian tube, together with the fundus and the cervix uteri, is a segment of the Müllerian duct system and its epithelium, like theirs, is of coelomic origin, the cervix uteri is the portion of the female generative tract most frequently involved, the Fallopian tube the portion least frequently involved in malignant disease.

This is well shown by Haupt¹ who found 3 instances (0.22 per cent) of primary tubal cancer among 1,361 cases of all types of genital cancer in von Franqué's clinic. On the other hand, Schmidt² reported 10 instances (1 per cent) of primary tubal cancer among 995 genital cancers operated upon at the University Frauenklinik in Berlin.

The first case of primary tubal cancer to be described adequately was reported in 1886 by Orthmann.^{3†} While many attempts have been made to assemble the case reports that have accumulated in the literature since then, the results obtained vary considerably. An accurate appraisal of the total number of primary tubal cancers is not easy to make when one realizes, as has been stressed by Doran⁴ and others, that the same case may be reported separately by more than one author, that reported cases may be overlooked, and that cases of questionable acceptability may be included. To illustrate the foregoing, a few of the numerous excellent compilations that have appeared from time to time are cited; namely, those of Doran,⁴ Fromme and Heynemann,⁵ Dietrich,⁶ Wechsler,⁷ Liang,⁸ Vest,^{9, 10} Wharton and Krock,¹¹ Nürnberger,¹² Harms,¹³ Robinson,¹⁴ and Schmidt.² All of these reveal the same unavoidable discrepancies. It should be noted, however, that Nürnberger in his critical study was able to compile 301 cases up to and including the first part of 1931. As far as we can ascertain, by the end of 1935 the total number of reported cases varied from 331 to 349. From 1935 to 1938 inclusive, we were able to collect from the *Cumulative Index Medicus* reports of 32 new cases by the following authors: 1 case each by Wlassow,¹⁵ Stolz and Machátová,¹⁶ Beitzke,¹⁷ Dannreuther,¹⁸ Held,¹⁹ Powers and Harrison,²⁰

*Read at the Sixty-Fifth Annual Meeting of the American Gynecologic Society held at The Seignior Club, Quebec, Canada, June 17 to 19, 1940.

†This reference gives a microscopic study. Many authors, however, refer to a later publication by Orthmann under the impression that the reference here cited gives inadequate data.

surgery alone. With regard to the low grade lesions, radiation, in our experience, has been equally as effective as surgery alone, or as effective as combined radiation and surgery.

Our results are not as good as Dr. Miller's. As a matter of interest I have tabulated the results according to the grade of malignancy and to the type of treatment, not with the idea of drawing conclusions but merely to show trends. These tables are appended (Tables I, II and III).

TABLE I. RESULTS OF TREATMENT OF FUNDAL CARCINOMA

62 Patients seen, 1 untreated, 100% follow-up

Five-year salvage (Including cancer deaths)	25 patients	40.9% 40.3%
Five-year salvage (Excluding cancer deaths)	21 patients	33.8% 34.4%
Five-year salvage (Now alive, 5 to 15 years)	15 patients	24.1% 24.5%

TABLE II. FIVE-YEAR SALVAGE IN RELATION TO TYPE OF TREATMENT

TYPE OF TREATMENT	NUMBER OF PATIENTS	INCLUDING CANCER DEATHS	EXCLUDING CANCER DEATHS	PRESENT-DAY SALVAGE
Radiation and surgery	18	8 (44.4%)	6 (33.3%)	5 (27.7%)
Radiation	30	14 (46.6%)	12 (40.0%)	7 (23.3%)
Surgery	13	—	—	3 (23.0%)

TABLE III. FIVE-YEAR SALVAGE IN RELATION TO GRADE OF MALIGNANCY

GRADE OF MALIGNANCY	NUMBER OF PATIENTS	INCLUDING CANCER DEATHS	EXCLUDING CANCER DEATHS	PRESENT-DAY SALVAGE
Low	19	13 (57.8%)	11 (61.3%)	9 (47.3%)
Intermediate	24	6 (25.0%)	4 (16.6%)	2 (8.3%)
High	17	—	5 (29.4%)	3 (17.6%)

(One patient unclassified, alive 15 years)

DR. KARL H. MARTZLOFF, PORTLAND, OREGON.—I would like to ask Dr. Miller whether the anatomic specimens which he obtained following preoperative x-ray radiation showed the same degree of cancer destruction as after intrauterine radium irradiation? It seems to me that if the destruction of the cancer is the primary object, then intrauterine radium irradiation is the method of choice. If the rationale of deep x-ray therapy is primarily for its effect upon the uterine circulation, then of course I can see his intention there. Certainly Dr. Miller's excellent salvage statistics bear out the correctness of his procedure.

DR. MILLER (closing).—In reply to the question raised by Dr. Martzloff, it may be said that the neoplasm is decidedly affected by preoperative radiation regardless of type. Probably the intracavitary radium gives a greater local reaction than the externally applied x-ray. The latter, however, is evenly distributed whereas the intracavitary radium may be very active in one area and leave another portion unaffected.

and relieved by vaginal discharge; and site, shape, and rapid development of the tumor. Others have emphasized sacral pain, back pain, and pain radiating along the sciatic or femoral nerves, obviously symptoms too unspecific to be of help.

An analysis which we made of 233 of the 301 cases tabulated by Nürnberger and of 31 of the 32 cases reported from 1935 to 1938 indicates that clinically these patients with primary cancer of the Fallopian tube can be divided into two groups: (1) those who have no abnormal vaginal discharge, and (2) those who have an abnormal vaginal discharge. In the first group, irrespective of whatever other symptoms and signs are present, there is little to warrant clinical differentiation from other types of adnexal disease.

The second group comprises somewhat more than half of the analyzed cases. In about one-fifth of these, the discharge was described merely as "leucorrhea," obviously not a symptom to arouse suspicion in view of its frequency and varied manifestations.

In about two-fifths of these cases, the discharge was described as bloody, and had occurred as a metrorrhagia during the menstrual life of the patient or after the menopause. Diagnostic curettage, judging from our analysis of these cases, ordinarily gives no clue to the underlying pathology,* and in the absence of abnormal manual pelvic findings may lull one into a sense of false security. In fact, abnormal uterine bleeding, though associated with physical findings that signify abnormality of the intra-abdominal generative tract, obviously is not sufficiently suggestive to warrant suspecting cancer of the tube. The same may be said of pelvic pain. Intermittent, cramplike discomfort, however, when not related to menstruation or to some of the atypical forms of postovulatory, intermenstrual discomfort, may be a helpful diagnostic symptom when it is followed and relieved by a blood-tinged, watery discharge, as occurred in one of the patients of Anspach and Hoffman.⁴³

In another one-fifth of the cases, there was a history of either a profuse serous or watery vaginal secretion, a symptom in itself difficult to evaluate prior to the establishment of an anatomic diagnosis. It is a symptom which Doran and others have noted, and, of course, one which raises the old argument of the possible existence of a benign hydrops tubae profluens. Hydrops tubae profluens probably does occur in those patients with cancer of the tube who have a profuse serous or sero-hemorrhagic vaginal discharge.

The remaining one-fifth of the cases, in our opinion, were those offering diagnostic promise. In these, bloody discoloration of the watery (serous) secretion was recorded. This represented not only secretion from the tubal epithelium, but also, probably, the products of autolytic change secondary to tumor necrosis, capillary damage, transudation, and hemorrhage. Obviously, few symptom-sign complexes are diagnostic of a malignant visceral neoplasia. However, if one can exclude recent gestation and organic disease of the vagina and uterine cavity, especially

*In a rare instance in which extension of the cancer to the endometrium has occurred, as reported by Smith,⁴¹ Kittler,⁴² Lenczowski,²⁹ or Wharton and Krock,¹¹ diagnostic curettage might reveal a cancer. Ordinarily this would be, and has been, confused with primary endometrial malignancy.

Janota and Reček,²¹ Sarikadioglu,²² Phaneuf,²³ Jeanneney and Soubiran,²⁴ Müller,²⁵ Altkaufner and Szejnberg;²⁶ 2 cases each by Robinson,¹⁴ Harms,¹³ Charache,²⁷ Bazterrica and others;²⁸ 3 cases by Lenczowski;²⁹ and 9 cases by Schmidt.² These reports were all verified by consulting the original sources.*

INCIDENCE

Once attention is focused on a given process its apparent earlier rarity appears to diminish in the face of its more frequent recognition. Schroeder³¹ was of the opinion that primary cancer of the Fallopian tube never occurred. According to various estimates in the literature, the incidence ranges from 1.33 per cent (Zangemeister³²) to 0.34 per cent (Martin³³) of operations on diseased tubes. We have been unable to verify the figures attributed to Martin.

It is generally overlooked that the often quoted figures of Zangemeister are derived from a twelve-year compilation of operative material from the University Frauenklinik, Leipzig. In this study 5 instances of cancer of the tube were found among 374 operations for various types of tubal disease. While this gives an incidence of 1.33 per cent, it is well to remember that the material represents an annual average of about 31 operations. That this is probably a fortuitous circumstance is suggested by the experience of Danckwardt³⁴ who found one primary tubal cancer among 5,000 gynecologic laparotomies performed in the same clinic from 1926 to 1932. For the thirty-four-year period prior to 1926, according to Zweifel,³⁵ only 7 instances of this disease had been seen in the same clinic. Frankl³⁶ stated that he had seen 12 instances over a period of twenty years, while Askanazy³⁷ had observed only two examples in his laboratory over a period of thirty-five years. Bazterrica and others²⁸ reported 2 instances (0.45 per cent) among 437 cases of tubal affection. Eleven cases were encountered in the Gynecologic Clinic of the Johns Hopkins Hospital during the fifty years of the hospital's existence. Five of these had occurred prior to 1929.¹¹ From January, 1930, to January, 1940, according to TeLinde,³⁸ 6 more cases were found among 14,365 gynecologic operative specimens. It appears probable, therefore, if one allows for unreported as well as unrecognized cases, that the upper limit of primary tubal cancer incidence may be in the neighborhood of 0.5 per cent.

CLINICAL DIAGNOSIS

It has been stated repeatedly that the diagnosis of primary cancer of the Fallopian tube has never been made before operation. Undoubtedly exceptions have occurred.† On the other hand, Fonyó⁴⁰ stated that up to the time of his study cancer of the Fallopian tube was diagnosed in only 6.5 per cent of the reported instances. Without attempting to reconcile these two opposing points of view, we wish to point out that in a certain small group of patients a tentative clinical diagnosis of primary cancer of the Fallopian tube can be made with a fair degree of accuracy. This is illustrated by the case herein reported.

Various authors have attributed diagnostic import to age; the patient's state of nutrition; intermittent, localized, cramplike pain followed

*The publication by Leuret,³⁰ while indexed, is not included here since no case report is presented. The case of Sarikadioglu²² is so briefly reported that its acceptability may be questioned.

†Hoffman³⁹ stated that a definite diagnosis was made in one of the cases reported by Anspach and himself. Dannreuther³⁸ also stated that in his case the suspicion of primary tubal malignancy was confirmed by operation.

TABLE I. CASES REPORTED SINCE 1935 WHERE AUTHORS USED OR ADVISED USE OF POSTOPERATIVE RADIATION THERAPY

AUTHOR'S NAME AND YEAR OF REPORT	NUMBER OF CASES	TYPE OF OPERATION	TYPE OF RADIATION THERAPY	TIME BETWEEN TREAT- MENT AND CASE REPORT	DURATION OF LIFE AFTER TREAT- MENT	LIVING AT TIME OF REPORT	NOW DEAD	REMARKS
Held (1935)	1	Salpingo-oophorectomy right	Radium, 7,200 mc.	1+ yr.	1+ yr.	0	+	No influence on dis- ease by radiation.
Beitzke (1935)	1	Hysteromyomectomy salpingo-oophorec- tomy	Roentgen	9 mo.	?	?	?	
Powers and Harrison (1935)	1	Supravaginal hysterec- tomy, salpingo- oophorectomy	Roentgen for recur- rence 3 yr. after operation	1 yr.	4+ yr.	+	+	Radiation did not in- fluence recurrent process. Died of generalized carci- nomatosis ³
Charache (1936)	2	(1) Left salpingectomy, appendectomy. One wk. later panhyster- ectomy, removal of remaining adnexa (2) Supravaginal hys- terectomy. Salpingo- oophorectomy	Roentgen, 1,720 units	1 yr.	3 yr.	+	+	Died of abdominal recurrence. ¹
Schmidt (1936)	9	(1) Panhysterectomy. Salpingo-oophorec- tomy (2) Panhysterectomy. Salpingo-oophorec- tomy	None Roentgen 2 series	5 yr. 3 yr.	2 yr. & 8 mo. 3 yr.	0 0	+	Died following oper- ation for intestinal obstruction, not due to malignancy ⁴

¹Personal communication from Dr. Herman Charache.²Personal communication from Dr. Louis E. Phaneuf.³Personal communication from Dr. John H. Powers.⁴Previously reported by Hornung, 1927.

incipient ulcerating cancer complicated by cervical stenosis, then a copious, serosanguineous uterine discharge becomes suspiciously pathognostic. For it can then be ascribed to an extrauterine origin, logically tubal, and a malignant complication may be inferred, as was done in our case.

Hysterosalpingography as an aid in diagnosis is not mentioned in the literature, and was not used by us. It should be of inestimable value, however, when no physical signs other than a vaginal discharge are detectable.

If, therefore, the possibility of an extrauterine lesion is kept in mind, and if, too, hysterosalpingography is utilized, the generally justifiable pessimism concerning the practicability of making a clinical diagnosis of primary cancer of the Fallopian tube should not extend to those patients presenting the syndrome of hemohydrops tubae profluens.

THERAPY

The question arises as to what constitutes adequate treatment. It is accepted that total hysterectomy and adnexectomy are logical procedures when feasible. The question also arises as to the advisability of using high voltage roentgen therapy after operation. This was not used on our patient, despite its recommendation by numerous writers, because of the absence of factual support for such a recommendation. After careful search of the literature, we are unable to find satisfactory evidence of its value. There are several reasons for the lack of satisfactory information concerning the value of deep roentgen ray therapy. Among these are: (1) The number of patients so treated, because of the infrequency of the disease, is, according to Burnam,¹¹ too small to warrant conclusions; (2) writers who report the cases of patients operated upon several years previously often do not report the status of their patients at the time of the report; and (3) the period between the treatment given a patient and the reporting of her case is in numerous instances too brief to allow an estimate of the ultimate outcome.

Table I illustrates the present status of this problem. It is seen here that 22 patients had received postoperative radiation treatment. Of these, 10 (45 per cent) were known to be dead, and 8 (36 per cent) were alive at the time of the report. In 7 instances (31 per cent), the outcome of the treatment was not stated. Of the 8 living patients, 5 had been alive less than one year, while 3 had been alive eight, three, and two years at the time of the reports. In brief, the information available here is too inadequate to warrant any conclusions as to the value of radiation therapy. Obviously an eight-year survival, as in Schmidt's Case 4, is not conclusive. The same may be said of Kaplan's⁴⁴ patient who lived somewhat over four years. Radiation treatment had been given to this patient five months after operation. While these cases are cited as encouragement for the combined use of surgery and radiation, the danger of drawing conclusions from such isolated experiences is clear when one compares them with the experience of Powers and Harrison.^{20, 45} Their patient lived over four years before manifesting a local recurrence which did not respond to radiation therapy. Furthermore, there are reports of patients who lived for long periods after operation without subsequent radiation therapy. Six of the patients in Nürnberger's¹² study lived five or more years without postoperative radiation treatment, while 14 lived three years. Jähkola⁴⁶ reported the case of one patient who was alive and well seven years (one patient who had had radiation therapy was living after six years). Haupt's¹ patient lived twenty years, Norris'⁴⁷

TABLE I—CONT'D

AUTHOR'S NAME AND YEAR OF REPORT	NUMBER OF CASES	TYPE OF OPERATION	TYPE OF RADIATION THERAPY	TIME BETWEEN TREAT- MENT AND CASE REPORT	DURATION OF LIFE AFTER TREAT- MENT	LIVING AT TIME OF REPORT	NOW DEAD	REMARKS
Altkauer and Szenjberg (1937)	1	Panhysterectomy. Salpingo-oophorec- tomy	Röntgen	Less than 1 yr.		+		
Müller (1937)	1	Panhysterectomy. Salpingo-oophorec- tomy	Röntgen	Less than 1 yr.		+		
Lenczowski (1938)	3	(1) Panhysterectomy. Salpingo-oophorec- tomy (2) Panhysterectomy. Salpingo-oophorec- tomy (3) Panhysterectomy. Salpingo-oophorec- tomy.	Röntgen intensive Röntgen intensive Röntgen intensive	 Less than 1 yr.	? Less than 1 yr.	0 + +	+	
Bazterrica et al. (1938)	1	Panhysterectomy. Salpingo-oophorec- tomy	Röntgen	7 yr.	Not stated	?	?	No statement con- cerning patient's status
Jeanneney and Soubiran (1938)	1	Supravaginal hysterec- tomy. Left Salpingo- oophorectomy	Recommend radiation but say nothing of its use on this pa- tient	Less than 1 yr.	?	?	?	No statement con- cerning patient's status.
Phaneuf (1938)	1	Panhysterectomy. Salpingo-oophorec- tomy	Röntgen 6,200 R.U.	1+ yr.	9 mo.		+	Extensive involve- ment. Died of metastatic carcino- matosis. ²

Janota and Reček (1936)	1	(3) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen 2 series	?	3 mo.	0	+	Peritoneal implants present at time of operation.
		(4) Right salpingo- oophorectomy	Roentgen 2 series	8 yr.	8 yr.	+	0	
		(5) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen 2 series	7 yr.	3-4 yr.	?	?	
		(6) Hysterectomy. Right salpingo- oophorectomy	Roentgen 2 series	7 yr.	7 wk.	0	+	
		(7) Panhysterectomy. Salpingo-oophorec- tomy	Radium for recurrence	4 yr.	?	0	+	
		(8) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen	3 yr.	3 yr.	+		
		(9) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen 3 series	2 yr.	2 yr.	+		
		(10) Panhysterectomy. Salpingo-oophorec- tomy Nov., 1935	Radium Sept., 1935 for cancer of cervix. Roentgen after operation	Less than 1 yr.	Less than 1 yr.	÷		
		Panhysterectomy. Salpingo-oophorec- tomy	Roentgen	3 yr.	3 yr.	+	0	
Harms (1937)	2	(1) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen castration 6 mo. preoperatively	?	?	?	?	Both patients had diagnostic curettage for bleeding. Roent- gen ray for pre- sumed benign met- rorrhagia.
		(2) Panhysterectomy. Salpingo-oophorec- tomy	Roentgen castration preoperatively	?	?	?	?	

Prognosis poor,
signs of recurrence
present at time of
report.

fornix. The mass was adherent but not fixed. It was felt that the process now was one of borderline operability, probably inoperable. A provisional diagnosis of cancer of the Fallopian tube was made, and operation was again advised.

Operation.—Six days later (Aug. 11, 1936) a supravaginal hysterectomy and right salpingectomy were performed. The essential finding at operation, aside from numerous parietovisceral and viscerovisceral adhesions which made the operation difficult, was the densely adherent right tube. In situ the tube measured about 8 cm. in diameter in its ampullar portion. It resembled an ordinary hydrosalpinx, and so overlay the small uterus as to completely obscure it. For purposes of exposure, it was expedient to remove the tube separately, the tubal section being performed between hemostats in the grossly normal isthmic portion. A supravaginal hysterectomy was done in preference to a total removal, despite the suspicion of tubal malignancy, because this procedure was simpler and safer in the presence of the existing anatomic distortion and adhesions. The tube as removed was grossly intact. No left tube or ovary was demonstrable, while a right ovary could not be identified. No palpable retroperitoneal glands were felt, and there was no gross evidence of peritoneal carcinomatosis. Convalescence was uneventful, and the patient was discharged from the hospital on the eleventh postoperative day. She was last seen in March, 1940, at which time she felt well and was gaining weight. Abdominal and pelvic examinations were irrelevant.*

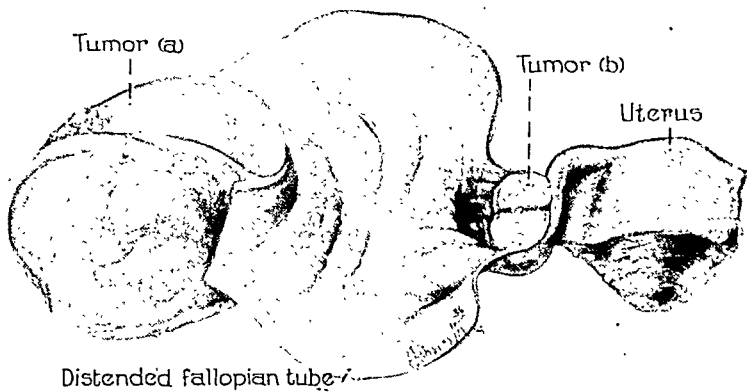


Fig. 1.—Illustrating primary carcinoma of right Fallopian tube. Primary tumor at *a*. Distended Fallopian tube has been opened longitudinally and is seen to retract from Tumor *a* where the latter is unattached and projects into the lumen of the tube. Secondary tumor at *b* occluding lumen of tube.

Pathologic Study.—Gross Examination: The fresh, gross, tubal specimen, examined immediately after the completion of the operation, resembled an ordinary hydrosalpinx with a closed fimbriated end. Except for numerous fibrous tags, its surface was smooth. Over the point represented as Tumor *b* in Fig. 1, the tube decreased rather suddenly in caliber. Beyond this point the isthmic portion of the tube was of about normal caliber. Incision of the distended portion of the tube released a copious amount of watery, blood-stained fluid, while the infundibular portion revealed a soft, yellowish gray, friable material.

The shrunken, formalin-fixed specimen measured 9.5 cm. in length and from 1.5 to 4.5 cm. in diameter in its enlarged portion. At what corresponded to the infundibular portion of the tube was a tumor mass (*a*, Fig. 1) measuring 5.5 by 3.5 by 4 cm. The mass was softly elastic and smooth, and its serosa presented no evidence of neoplastic involvement. On section, the wall of the tube retracted immediately from the tumor proper. The cut surface of the tumor was yellowish

*Since preparation of this paper the patient has developed a left-sided cervical lymphadenopathy. Tissue removed for biopsy revealed an obvious metastatic carcinoma resembling the section shown in Fig. 6. Pelvic, abdominal, and laryngoscopic examinations and roentgenographic examination of the chest are at present irrelevant. Satisfactory temporary response has occurred to roentgen ray therapy.

lived nineteen years, Dannreuther's⁴⁸ lived six years, and Wharton's⁴⁹ lived thirteen years without radiation therapy. Wharton and Krock¹¹ reported the case of a patient who had died after five years, but not of cancer. They also reported the cases of 2 patients who had been alive and well four and three years, respectively, at the time of their study.

CASE REPORT

History.—Mrs. M. D., white, aged 54 years, was first seen on May 2, 1931 because of a bloody vaginal discharge. Her family history was irrelevant. In 1915 she had had a left salpingo-oophorectomy, in 1920 an appendectomy, and in 1924 a cholecystectomy. She had never been pregnant, and had ceased menstruating in 1924, at the age of 47. No further vaginal bleeding had occurred until one year prior to consultation (six years after the menopause) when she had begun to have a scanty, intermittent, odorless, bloody, vaginal discharge.

Physical Examination.—The vagina contained a slightly blood-stained secretion. The uterus was felt to be small, symmetrical, and in second degree retroposition. The parametrial regions presented no notable change, and the right ovary could not be outlined. The remainder of the examination and routine urine and blood examinations, including a Wassermann test, were of no significance.

Impression.—The clinical impression was postmenopausal metrostaxis of undetermined origin.

Diagnostic curettage on May 6, 1931, produced no grossly identifiable endometrial tissue. Microscopic examination of the cervical tissue which had been excised showed no noteworthy pathology. Pelvic examination under anesthesia at this time was not noteworthy. The uterine canal measured between 3.5 and 4 cm. in length. There was no evidence of cervical stricture.

Subsequent Course.—Each speculum examination following the curettage revealed some blood in the vagina, of which the patient was not cognizant. About a month after the curettage the patient again noted a bloody vaginal discharge. She continued to bleed regularly though intermittently, having an occasional day with no bleeding. Speculum examination two and a half months later revealed a brownish, watery discharge coming from the cervical canal. The passage of a sound into the cervical canal and the bimanual examination were not noteworthy. A note was made at this time that while this postmenopausal bleeding might be caused by an uncomplicated, local, endometrial, vascular process, in view of the watery character of the discharge, the possibility of tubal malignancy should not be overlooked and the possibility of a nonpalpable ovarian neoplasm (granulosa cell tumor) should be considered. The patient felt well and was gaining weight. She was examined once more in March, 1932; then was not seen again until July 1, 1935.

The history at this time was unchanged except that during the four months before July, 1935, she had felt she was losing urine from the bladder in small involuntary gushes. Examination revealed a blood-tinged watery secretion. A uterine sound met obstruction at about the level of the internal os which was passed with some difficulty. The uterine cavity now measured approximately 6 cm. in length. There was no evidence of pent-up secretion. Upon bimanual examination a tender, smooth, adherent, somewhat elastic mass, measuring about 4 to 6 cm., was noted in the right cul-de-sac. Cystoscopic examination was irrelevant. Five cubic centimeters of methylene blue were left in the bladder without evidence of methylene blue leakage per vaginam. The impression was again recorded that this was probably a cancer of the right Fallopian tube, and operation was advised. An ovarian cyst, however, could not be excluded. The increased length of the uterine cavity, together with the difficulty of passing a uterine sound, suggested a partial cervical stenosis.

On Dec. 10, 1935 the patient gave the same history and stated that she felt well. The findings were also the same. Operation was again advised.

The patient returned on Aug. 5, 1936, stating that she had been severely jarred in an automobile accident seven weeks previously. One week after the accident the blood-tinged watery discharge had ceased, and since then there had been considerable abdominal discomfort of a constant, dull, aching character. Examination was essentially the same as before, except that the right pelvic mass now bulged into the right lateral vaginal fornix, and there was induration in the right posterior

a for here the cells occurred in broad strands and compact alveoli (Fig. 6). There was no necrosis, and the musculature of the tube showed discrete, dense aggregations of lymphocytes.

Sections from the isthmic portion of the tube proximal to Tumor *b* showed no evidence of anatomic abnormality.

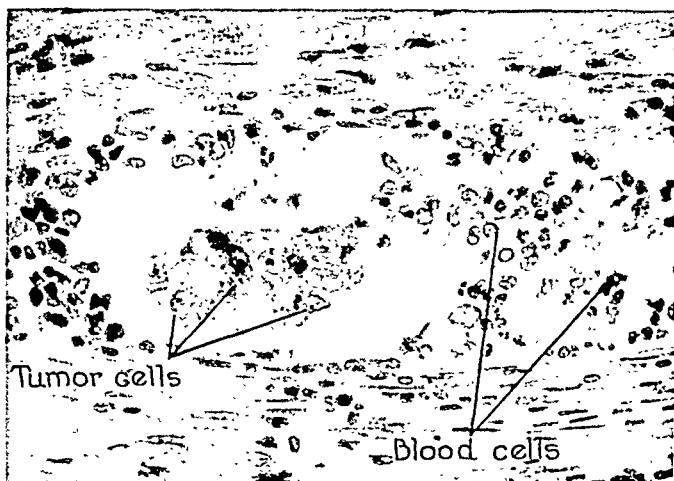


Fig. 3.—High power of blocked area in Fig. 2 ($\times 480$).

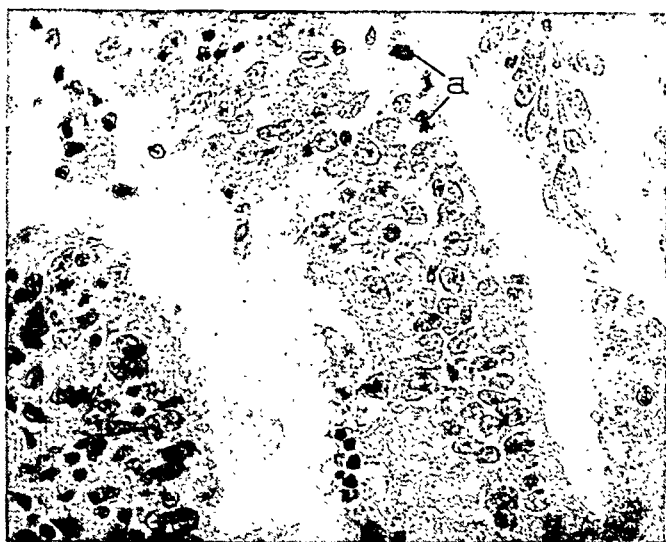


Fig. 4.—High power of tumor in Fig. 2 showing multilayered tumor cells. Mitoses at *a* ($\times 480$).

Sections from the uterus revealed the endometrium to vary from the minor fraction of a millimeter to over a millimeter in thickness. The glands varied from narrow straight tubules to moderately tortuous structures with moderately widened lumina. All were lined with columnar epithelium. In addition, there were numerous large, dilated glands which in general were lined by a single layer of epithelium varying from low columnar to flat. No mitotic figures were seen. The interglandular stroma had the appearance of fibrous connective tissue, and in its superficial portion showed the picture of bona fide endometritis.

Pathologic Diagnosis.—Primary carcinoma (papillary) of the right Fallopian tube associated with a secondary, intralumenary-occluding tumor nodule and hydrosalpinx; salpingitis, chronic, probably secondary to neoplastic change; senile atrophy of the uterus; endometritis, chronic; glandular hyperplasia of the endometrium (?).

gray and opaque. There was a central area of hemorrhage and a narrow peripheral zone which was gray, glistening, and translucent. Over this zone the tumor was adherent to the tubal wall.

The previously distended portion of the tube had shrunk considerably. It had a slightly corrugated, pale gray, and glistening mucosa, and measured 6 cm. in circumference and 1 to 1.5 mm. in thickness. At the extreme uterine end of this dilatation, there was a smaller tumefaction (*b*, Fig. 1) which measured 1.5 by 1.5 by 1.8 cm. It appeared to be well circumscribed, confined within the lumen of the tube, and on section presented a pale gray, glistening, translucent surface.

The uterus was small, measuring 3.5 by 2.8 by 2 cm. In the fixed specimen the uterine cavity measured 2 cm. in length, and the myometrium 0.8 cm. in thickness. The endometrium was smooth and could be seen distinctly. In its thickest portion it measured about 1.5 mm.

Histologic Examination: Sections through the tube wall and Tumor *a* (Fig. 1) showed Fallopian tube muscularis along one side; occasional moderately dense aggregations of mononuclear white blood cells, some of the plasma cell type, in the inner half of the tube wall; and only a scanty lymphocytic infiltration in the outer half of the wall. The serosa was not definitely identifiable.

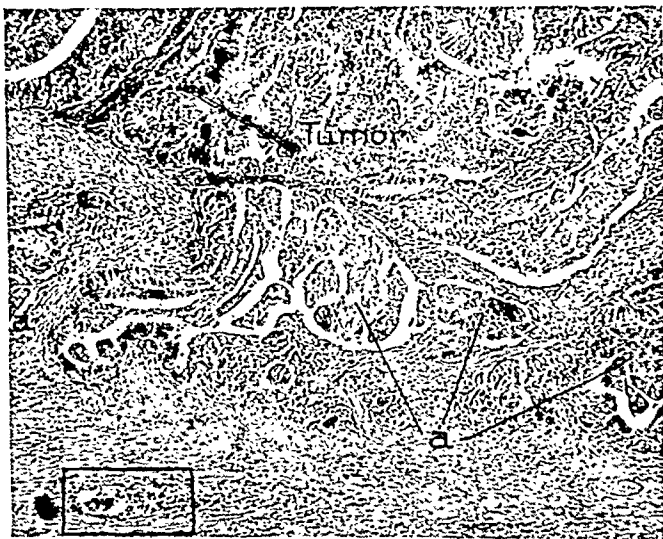


Fig. 2.—Section from Tumor *a*, Fig. 1, and wall of attached Fallopian tube. Blocked area is a blood vascular space containing tumor cells. *a* indicates tumor process invading wall of tube ($\times 60$).

The luminal aspect of the sections showed an obvious neoplasm with a papillary arrangement (Figs. 2 and 4). The papillae were composed of central connective tissue cores with capillaries, dense round (plasma) cell infiltration, and a peripheral epithelial covering of large round and fat spindle-shaped cells several layers in thickness. These cells were irregular in size, shape, staining reaction, and polarity. The chromatin distribution was coarse and often scanty. Nucleoli occurred but were not constant, while mitotic figures were abundant. Toward the center this cellular area ceased abruptly to pass over progressively into a zone of inflammatory change and then a zone of necrosis. Only the inner half of the tubal wall showed invasion. A few psammoma bodies were noted in the areas of round cell infiltration of the tumor interstitium and also in the more central area of necrosis.

Sections from the thin-walled, fluid-containing portion of the tube showed a slightly undulating inner surface (Fig. 5) lined by a single layer of flat or low columnar cells. Only a rare club-shaped fold was seen. A moderate subepithelial round cell infiltration also involved the remainder of the tube wall.

Sections from the smaller Tumor *b* showed a cytology similar to that in the larger Tumor *a*. However, its papillary character was not so obvious as in Tumor

It also cannot be definitely stated whether the endometritis was secondary to contact with the products of tumor degeneration passing from the tube into the uterine cavity or secondary to a possible cervical stenosis.

SUMMARY AND CONCLUSIONS

A case is reported of primary carcinoma of the Fallopian tube which was tentatively diagnosed before operation. The patient is alive and well four years after operation (see footnote, p. 812).

The symptoms and signs of this comparatively rare disease, as one obtains them from the literature, are so protean, and in general so similar to other types of adnexal disease that there is little logical basis for suspecting its existence.

A tentative diagnosis of primary carcinoma of the Fallopian tube, however, can logically be considered in that limited group of patients who present the syndrome of hydrops tubae profluens with a sero-sanguineous vaginal discharge but no causative vaginal or uterine pathology.

Hysterosalpingography should have a definite place in the establishment of a provisional clinical diagnosis, especially if palpable pelvic abnormality is not demonstrable.

The high degree of malignancy of this disease, as generally stated in the literature, is in some instances probably more apparent than real when one considers, as in the case herein reported, the long duration of the disease before operation.

The use of high voltage roentgen ray therapy is recommended by numerous authors. However, there is at the present time no suitable information available that indicates its value in the treatment of this disease.

REFERENCES

- (1) *Haupt, W.*: Zentralbl. f. Gynäk. 57: 742, 1933. (2) *Schmidt, Kurt*: Ztschr. f. Geburtsh. u. Gynäk. 112: 339, 1936. (3) *Orthmann*: Zentralbl. f. Gynäk. 10: 815, 1886. (4) *Doran, A.*: J. Obst. & Gynaec. Brit. Emp. 17: 1, 1910. (5) *Fromme, F., and Heynemann, T.*: Veit's Handb. d. Gynäk. 5: 182, 1910. (6) *Dietrich, H. A.*: Die Neubildungen der Eileiter, Biologie und Pathologie des Weibes, Berlin, 1926, Halban-Seitz 5: Part 1, p. 13. (7) *Wechsler, H. F.*: Arch. Path. 2: 161, 1926. (8) *Liang, Z.*: Virch. Arch. f. path. Anat. 259: 577, 1926. (9) *Vest, C. W.*: Johns Hopkins Hosp. Bull. 25: 305, 1914. (10) *Vest, C. W.*: Malignant Growths on the Fallopian Tube, in Lewis' Loose Leaf Surgery, Hagerstown, Md., 1927, W. F. Prior Co., Inc. 2: Chapt. 1, p. 1. (11) *Wharton, L. H., and Krock, F. H.*: Arch. Surg. 19: 848, 1929. (12) *Nürnberg, L.*: Veit-Stoeckel Handbuch der Gynäkologie, ed. 3, 7: 679, 1932. (13) *Harms, C.*: Zentralbl. f. Gynäk. 61: 2628, 1937. (14) *Robinson, M. R.*: AM. J. OBST. & GYNEC. 32: 84, 1936. (15) *Wlassow, W.*: Monatschr. f. Geburtsh. u. Gynäk. 98: 217, 1934. (16) *Stolz, J., and Machátová, O.*: Bratisl. lekár. listy. 15: 465, 1935. (17) *Beitzke, H.*: Schweiz. med. Wehnschr. 65: 513, 1935. (18) *Dannreuther, W. T.*: AM. J. OBST. & GYNEC. 30: 724, 1935; personal communication, 1939. (19) *Held, E.*: Gynéc. et obst. 32: 395, 1935. (20) *Powers, J. H., and Harrison, F. F.*: Clin. Misc. Mary I. Bassett Hosp. 2: 30, 1935. (21) *Janota and Reček*: Casop. lék. česk. 75: 1205, 1936. (22) *Sarikadioğlu, Halis Tevfik.*: Türk tib cem. mec. 3: 156, 1937. (23) *Phaneuf, Louis E.*: Am. J. Surg. 39: 620, 1938. (24) *Jeanneney and Soubiran*: J. de méd. de Bordeaux 115: 5, 1938. (25) *Müller*: Spisy lék. fak. Masaryk. Univ. 16: 57, 1937. (26) *Altkauf, H., and Szejnberg, H.*: Ginek. polska 16: 924, 1937. (27) *Charache, H.*: Ann. Surg. 103: 290, 1936. (28) *Bazterrica, E., Barcas, E., and Ferracani, R. S.*: Rev. méd.-quir de pat. fem. 12: 439, 1938. (29) *Lenczowski,*

Clinical Pathologic Summary.—The neoplasm represents a primary carcinoma of the Fallopian tube occurring in a woman past the menopause, whose symptoms were of six years' duration, who was under observation for five years, and whose condition was tentatively diagnosed a year before operation. The diagnosis was based on the history and the observation of a watery, blood-stained cervical discharge unexplained by diagnostic curettage and physical examination.

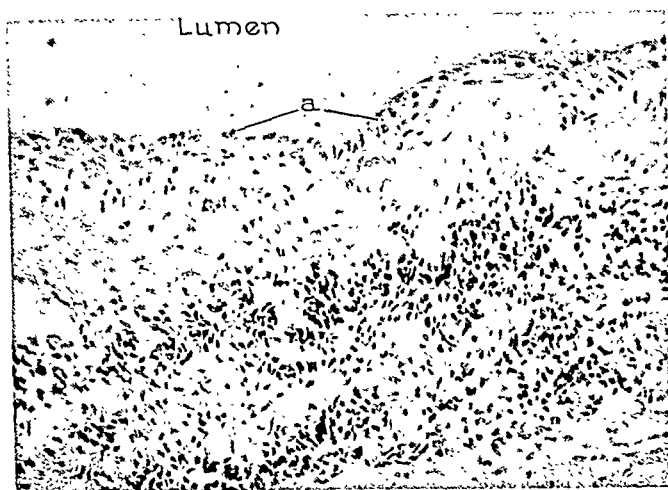


Fig. 5.—Section through wall of distended Fallopian tube, showing at *a* single layered flattened and cuboidal epithelium. Aggregations of leucocytes further out in tube wall ($\times 235$).

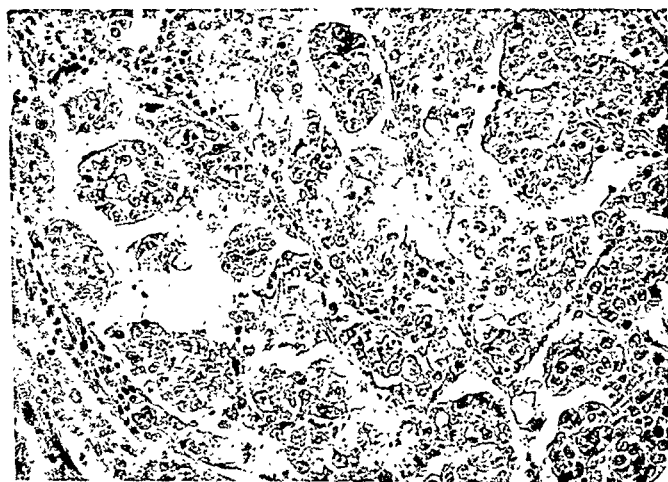


Fig. 6.—Section through Tumor *b*, Fig. 1 ($\times 235$).

It is impossible to say whether this patient's initial bleeding originated from an incipient tubal neoplasm or whether it represented a coincidental endometrial hemorrhage, as occurs in some forms of benign postmenopausal bleeding. However, in view of the uninterrupted character of the bleeding, and its gradual evolution to a predominately serous discharge, it is probable that it originated in the tube. The peripheral necrosis of the parent Tumor *a* explains the source of the serous, blood-stained secretion and the secondary phenomenon of hydrops tubae profuens which became increasingly profuse apparently as the size of the tumor and its degenerative changes progressed. The sudden cessation of the discharge one week after an injury is explained by the development of the secondary Tumor *b* which occluded the tubal lumen. Whether Tumor *b* represents a free tumor transplant, a metastatic process, or a separate malignant focus cannot be definitely determined.

walnut and appeared to be hemorrhagic. The involvement became less marked from this point toward the torn fimbriated end.

The uterus and both adnexa were removed. The pathologic report was primary adenocarcinoma of the left tube with implantation and lymphatic metastases to the uterus, right tube, and the large left ovarian cyst.



Fig. 1.—Hystero-gram with 2 c.c. of contrast medium. Note the irregular ragged outline of the uterine cavity.



Fig. 2.—Hystero-gram with 6 c.c. of contrast medium.

The follow-up notes show that despite postoperative x-ray therapy there were progressive weakness, weight loss, abdominal distention, epigastric distress, and five months after the operation general abdominal carcinosis. The patient was admitted to Dr. King's Hospital, Bay Shore, Oct. 16, 1933, where she died a month later. An autopsy was not made.

Bleeding in primary carcinoma of the tube without secondary involvement of the uterus presupposes patency of the tubal lumen. The lesion of the tube need not be necessarily large to cause bleeding, in which respect it resembles Paget's disease of the nipple where the papillary lesion is minute.

The outstanding symptom which differentiates papillary ovarian carcinoma from papillary carcinoma of the tube appears to be intermittent bleeding. I have rarely

J.: Ginek. polska 17: 517, 1938. (30) *Leuret, J.*: Gaz. méd. de France 44: 285, 1937. (31) *Schroeder, C.*: Handbuch der Krankheiten der Weiblichen Geschlecht-sorgane, ed. 2, Leipzig, 1875, p. 324. (32) *Zangemeister, W.*: Beitr. z. klin. Chir. 34: 96, 1902. (33) *Martin, A. E.*: Pathologie u. Therapie der Frauenkrankheiten, ed. 4, Berlin, 1907, p. 387. (34) *Danckwardt, L.*: Monatsehr. f. Geburtsh. u. Gynäk. 95: 84, 1933. (35) *Zweifel, E.*: Cited by Danckwardt, Ref. 34. (36) *Frankl, O.*: Henke-Lubarsch Handb. d. Spez. Path. Anat. u. Hist. 7: 847, 1930. (37) *Askanazy*: Cited by Liang, Ref. 8. (38) *TeLinde, R. W.*: Personal communication, 1940. (39) *Hoffman, J.*: Discussion, AM. J. OBST. & GYNEC. 26: 360, 1933. (40) *Fonyó, J.*: Zentralbl. f. Gynäk. 37: 1317, 1913. (41) *Smith, W. S.*: AM. J. OBST. & GYNEC. 24: 267, 1932. (42) *Kittler, E.*: Zentralbl. f. Gynäk. 51: 971, 1927. (43) *Anspach, B. M.*, and *Hoffman, J.*: AM. J. OBST. & GYNEC. 22: 424, 1931. (44) *Kaplan, I. I.*: In discussion, Ref. 41. (45) *Powers, J. H.*: Personal communication, 1939. (46) *Jahkola, A.*: Acta Soc. med. fenn duodecim 16: 1, 1931. (47) *Norris, C. C.*: Discussion, AM. J. OBST. & GYNEC. 26: 358, 1933. (48) *Dannreuther, W. T.*: Personal communication, 1939. (49) *Wharton, L. R.*: Personal communication 1939 concerning case reported in 1929, Ref. 11.

808 MEDICAL DENTAL BUILDING

DISCUSSION

DR. ISIDOR C. RUBIN, NEW YORK, N. Y.—During the years 1928 to 1939 inclusive, 8,356 patients were admitted to the Gynecologic Service of Mt. Sinai Hospital. There were 410 cases of carcinoma of the female genital tract. One case of primary carcinoma of the Fallopian tube was encountered and 4 secondary cases.

In order to note the relative incidence of tubal carcinoma, it was compared with the incidence of carcinoma of the ovaries, uterus, cervix, and external genitalia (Table I).

TABLE I

	PRIMARY CASES	SECONDARY CASES
Carcinoma of ovary	125	12
Carcinoma of corpus uteri	88	4
Carcinoma of Fallopian tube	1	4
Carcinoma of cervix		151
Carcinoma of vagina		10
Carcinoma of vulva		14
Carcinoma of clitoris		1

Among the private patients, there were during 1928-1939, 333 cases of genital carcinoma. In 5 of this group the tubes were secondarily involved. In 2 cases because of metastatic involvement, the pathologist reported that the lesion was probably primary; and in only one case was an unequivocal diagnosis made of primary carcinoma of the Fallopian tube.

The case of primary tubal carcinoma on the Ward Service was referred by me to the hospital Jan. 11, 1933, with the diagnosis of a left-sided ovarian carcinoma. She was a 61-year-old unmarried woman, eight years after her menopause. She complained of lower abdominal pains for six months previous to her admission. The pains were located more often in the left than the right lower abdominal quadrant and were intermittent and cramplike in character. There were pelvic heaviness, frequent urination and constipation for two years and occasional slight bleeding from the rectum. There was no vaginal discharge.

At operation a left ovarian cyst the size of a grapefruit was found, adherent to the uterus, partly intraligamentous. The sigmoid and omentum were adherent to the cyst and about a quart of free amber colored peritoneal fluid was present. The left tube was found thickened and lay upon the anterior surface of the left ovarian cyst to which it was densely adherent. Its distal end was torn in the manipulation and appeared to contain soft, partially necrotic and perhaps carcinomatous tissue. Seven centimeters from the fundus it bulged to the size of a

negative. A hystero-gram was made with fractional filling of 2, 4, 6, and 10 c.c. contrast fluid. The differential contrast with 30 c.c. of carbon dioxide was strikingly suggestive.

Without going into the technical consideration and the question of possible dislocation of carcinoma, I believe that we may safely use hippuran or other analogous substances for this purpose.

Reflecting upon the rare occurrence of primary tubal carcinoma, despite the relatively great frequency of salpingitis, one wonders whether chronic inflammation has any etiologic importance. On the other hand, the question why the Fallopian tube enjoys this apparent immunity while other derivatives of the Müllerian tract are frequently attacked by carcinoma, must remain unanswered for the present.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—Dr. Martzloff's compilation was made at the end of 1938, and in February, 1939, Dr. D. Nelson Henderson reported 2 cases from our service, both of which had occurred within a period of fourteen months. Dr. Henderson has recently had another case in his private practice, as yet unreported.

The diagnosis always presents great difficulties. The most common symptom is vaginal bleeding, usually occurring in patients past the menopause. The patients in each of our reported cases were 57 years of age. The preoperative diagnosis on our second case was granulosa cell tumor of the ovary, made on the basis of post-menopausal bleeding, negative findings on curettage, and palpation of a small tumor, thought to be ovarian. When no tumor is palpable, the diagnosis is usually carcinoma of the fundus of the uterus, and diagnostic curettage may not always differentiate between these two conditions, as secondary involvement of the endometrium may occur. If no tumor is palpable, and diagnostic curettage is negative, the patient may be treated expectantly or by radiotherapy and valuable time may be lost.

The frequency with which tubal carcinoma is associated with evidences of previous inflammatory disease is apparent from the study of the literature. In both of our cases the gross appearance of the tubes suggested previous inflammatory disease, and one patient gave a history of a post-partum pelvic inflammation.

It is obvious that the prognosis is bad in all these cases, and the value of radiotherapy after operation has yet to be established. In our first case the diagnosis was not made even with the abdomen opened, and consequently a supravaginal hysterectomy with removal of tubes and ovaries was carried out. Twenty-two months later there was recurrence in the cervix, which was treated with radium and deep x-ray therapy, and the patient then remained well for two years before developing widespread secondaries. The second case was diagnosed at the time of operation, and a total hysterectomy done. She remained well for three years and then developed multiple secondaries.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—In the last year I have seen two cases of primary carcinoma of the tubes, both private patients. In one there were no symptoms whatever except abdominal pain and the finding of a palpable mass to one side of the uterus. The other patient had the typical history described, except that her intermittent discharge was not blood stained but watery in character. This patient had had three attacks of what appeared to have been pelvic inflammatory disease. She ran a fever over several weeks, then it subsided, and I saw her for the first time after this episode. Feeling a mass at the side of the uterus I made a diagnosis of inflammation. She remained comfortable without fever until two months later when she had another febrile attack. We observed her through the second attack of fever until the temperature subsided but the watery discharge continued. Surgery was decided upon. The preoperative diagnosis was pelvic inflammatory disease with possible hydrosalpinx, but we found a primary carcinoma of the tube.

There was no question about the primary site of the disease in either case. In the second the tube when removed looked like the ordinary pus tube but on opening it we were surprised to find it filled with a soft mass of carcinoma.

encountered a case of papillary ovarian carcinoma which gave rise to uterine bleeding. In the differential diagnosis one must exclude on the one hand granulosa cell tumors, and on the other hand the rare combination of uterine papillary carcinoma with metastatic ovarian papillary carcinoma and vice versa. Both conditions were stressed by Dr. Martzloff. In contrast to papillary adenocarcinoma, the granulosa tumor is rarely adherent. Hormonal assay may help to distinguish estrogenic bleeding from that due to carcinoma.



Fig. 3.—Hysteroscopy after 10 c.c. of contrast medium and 30 c.c. of CO₂. Note the defects in the configuration of the uterine cavity and the well-marked coating of the surface mucosa.

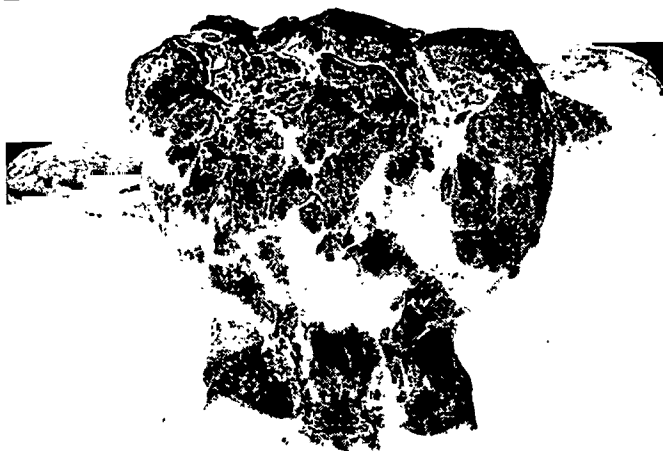


Fig. 4.—The carcinomatous uterus opened up; compare with Fig. 3.

A word as to uterotubal radiography in relation to malignancy which Dr. Martzloff thinks may be of value in differentiating uterine from tubal carcinoma. Since the availability of soluble crystalloid iodine compounds, I have again taken up injection of intrauterine radiopaque media as a diagnostic aid.

I wish to refer in this connection to a case in which carcinoma of the corpus was suspected. The patient was 49 years old, and began to bleed after three years of menopause. She bled for three months before her admission to the hospital. Her uterus was enlarged to the size of a six weeks' gestation while the adnexa were

FIBROMYOMA ANGIOMATOSUM OF THE UTERUS*

GEORGE H. GARDNER, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the Northwestern University Medical School and the Gynecologic Service of Passavant Memorial Hospital)

THIS is an interpretation of the unusual microscopic picture encountered in three submucous uterine tumors. Grossly, these tumors appeared to be partially degenerated fibroids. Microscopically they are composed of a smooth muscle and fibrous tissue stroma; however, there are few bundles of muscle fibers in transverse, longitudinal, and oblique sections, as is usual in a fibromyoma. Innumerable normally developed arteries are disseminated throughout these tumors and constitute their most striking microscopic characteristic; many of the arteries are quite large, others are small.

Such tumors are difficult to classify; they appear to be potentially malignant.

MATERIAL

TUMOR 1.—(I am indebted to Drs. H. O. Jones and John I. Brewer for the clinical data about this patient.) A 40-year-old nullipara was first admitted to St. Luke's Hospital in November, 1931, because of the usual systemic symptoms from a profound secondary anemia. A "fibroid polyp," the size of a small orange, presented in the external os and was removed by clamping and cutting its narrow pedicle.

She was readmitted in May of 1936, four and one-half years later, because of weakness and palpitation, again the result of marked secondary anemia. Fibromyomas were palpated in a uterus the size of a two and one-half months' pregnancy. Transfusions were given and a subtotal hysterectomy was performed. A soft polypoid tumor was found in the fundic portion of the uterine cavity; at its base there was invasion of the uterine muscle. This infiltrating tumor was sarcoma.

Her third admission occurred in November, 1937. The pelvis and lower abdomen were filled by firm tumor nodules; ascites was present; metastases were palpated in the vagina. She died in March, 1938, approximately six and one-half years after the vaginal myomectomy. The cause of death was generalized sarcomatosis, proved at autopsy.

Grossly, the original tumor, removed in 1931, was firm and spherical; red gray edematous tissue and streaks of yellow were noted on its cut surfaces. Microscopically, there is not much tissue which one can interpret as usual for a fibromyoma. The tumor appeared to be lobulated (see Fig. 1); each lobule was demarcated by a zone of necrotic tissue and consisted of an artery surrounded by a collar of pale-staining fusiform cells with elongated nuclei (see Fig. 2); these cells were arranged more or less radially in relation to the vessel. In the periarterial collars of essentially uniform-sized, pale-staining cells, one encounters an occasional mitotic figure.

There were several fibromyomas in the uterus removed in 1936, but the striking lesion was a soft gray polypoid tumor in the uterine cavity; it was attached to the fundus over a broad area. This tumefaction measured 6 by 4.5 by 4.5 cm. and, beneath it, tumor tissue invaded the uterine musculature. There was striking similarity, microscopically, between this necrotic polypoid tissue in the fundus of the uterus (see Fig. 3) and the original polypoid growth of 1931 (see Figs. 1 and 2). The tumor invading the myometrium was a typical spindle-cell sarcoma, with an abundance of mitoses.

*Presented, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Province of Quebec, Canada, June 17 to 19, 1940.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—There have been two specimens of primary carcinoma of the tube in my laboratory in the last five years. One, a private patient of mine, is alive and free from any recurrence four years after supravaginal hysterectomy and bilateral salpingo-oophorectomy.

I would like to ask Dr. Martzloff whether or not he feels that the exact diagnosis of adnexal tumor, suspected of tubal malignancy, is of sufficient importance to justify the use of any mechanical means in diagnosis, either lipiodol or gas? I have a feeling that there may be a very definite possibility of spreading cancer cells into the peritoneal cavity from such a procedure.

DR. MARTZLOFF (closing).—Dr. Sears' question of whether an exact diagnosis is sufficiently important to warrant hysterosalpingography, of course, raises a point that must occur to everyone. I would consider the procedure justified on the basis of what is commonly found at these operations. Dr. Watson stated that his clinical diagnosis was that of pelvic inflammatory disease, which is a situation frequently encountered. In our case the diseased tube at operation resembled a huge hydrosalpinx. In view of the fact that cancer of the Fallopian tube is so commonly associated with a perisalpingitis and occlusion of the abdominal ostium, hysterosalpingography carefully done is probably relatively safe and therefore desired in a patient who has this watery discharge and in whom nothing can be felt on examination. The need for early diagnosis probably outweighs the possible theoretical hazard of forcing cancer into the peritoneal cavity by this type of examination.

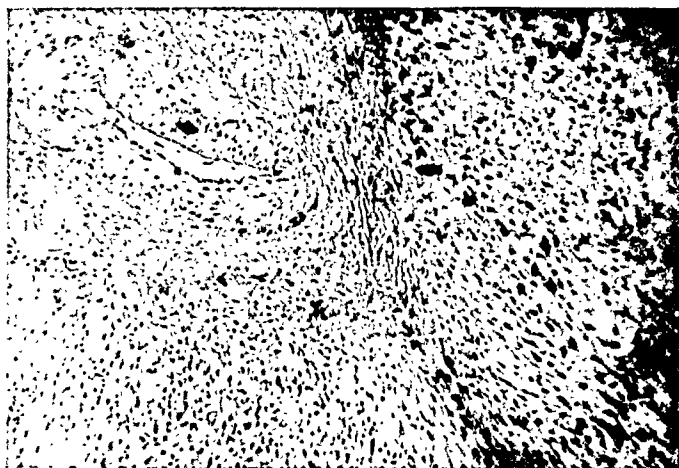


Fig. 3.—Necrotic polypoid tumor in the uterine cavity ($\times 70$). Note the striking similarity to the "polypoid fibroid" (see Fig. 1) removed four and one-half years previously. (Photographed by Clarence B. Mitchell.)

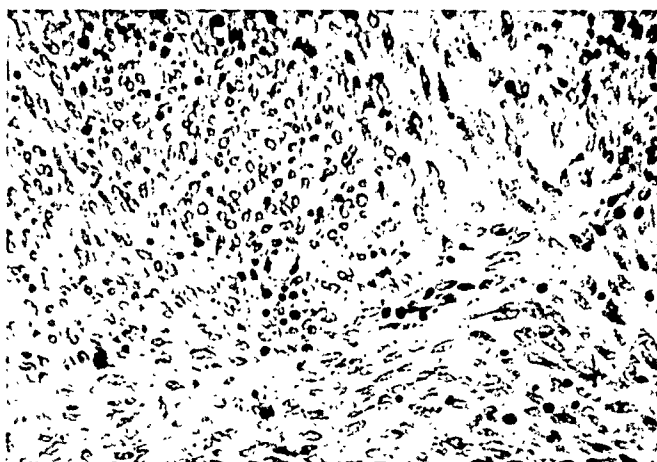


Fig. 4.—Vaginal metastasis of spindle-cell sarcoma ($\times 172$). (Photographed by Clarence B. Mitchell.)



Fig. 5.—(Tumor 2.) The arrangement of stromal cells is not typical for a uterine fibromyoma. The large number of normally developed arteries is striking ($\times 52$). (Photographed by Clarence B. Mitchell.)

The vaginal metastasis of 1937 was also a spindle-cell sarcoma (see Fig. 4).

TUMOR 2.—A 36-year-old para i, gravida i, not pregnant for thirteen years, was admitted to Passavant Memorial Hospital on Dec. 6, 1937, as a private patient of Dr. Arthur H. Curtis. (I wish to thank Dr. Curtis for permission to include these data.) She complained of profuse menstruation, and intermenstrual bleeding. A polypoid uterine tumor presented in the external os; it was excised.

Grossly this tumor was described as the size and shape of a cervical stump; it was solid and edematous. Microscopically there was almost a complete absence (see Fig. 5) of the usual whorl pattern of a uterine fibromyoma. The large number of thick-walled arteries was striking; between the vessels there were smooth

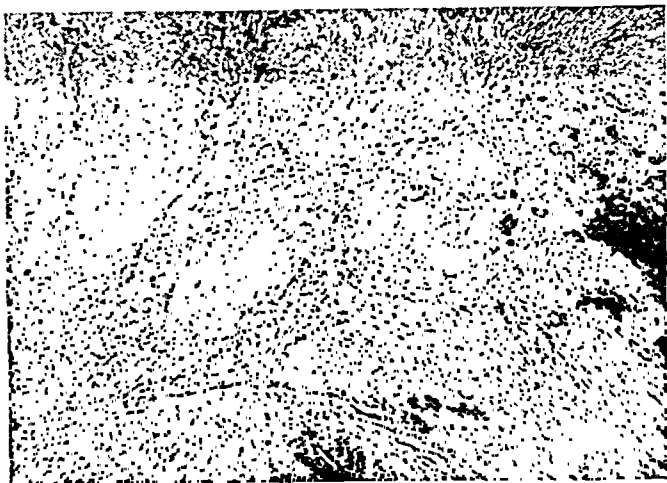


Fig. 1.—(Tumor 1.) This tumor appears to be lobulated ($\times 36$). (Photographed by Clarence B. Mitchell.)

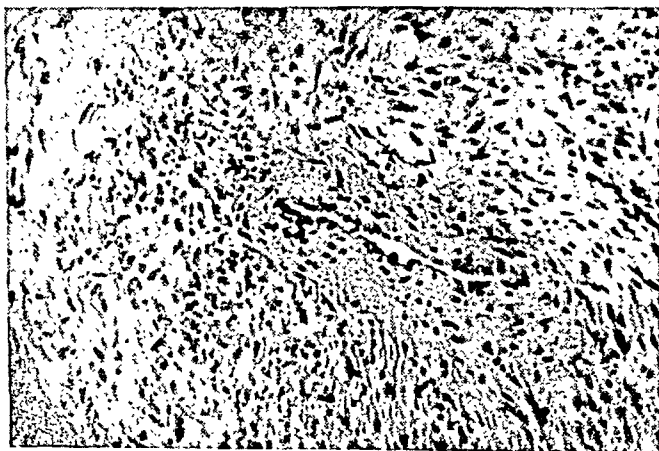


Fig. 2.—(Tumor 1.) A periarterial collar of pale-staining fusiform cells with elongated nuclei ($\times 108$). (Photographed by Clarence B. Mitchell.)

muscle fibers and fibrous tissue cells of fairly uniform size. In places the stroma was compact, elsewhere it was loose (see Fig. 6). There were a few zones of focal necrosis; in other areas the tumor was edematous. If one searches diligently he will find an occasional mitotic figure, but they are very rare.

In view of the peculiar microscopic appearance of this polypoid tumor and the clinical course of Tumor 1, Dr. Curtis advised his patient to return for a vaginal hysterectomy; this was performed on Jan. 6, 1938. Gross and microscopic study of the uterus failed to reveal anything abnormal. This patient is reported to be well.

it was solid, ivory in color, and through it there were streaks of gray gelatinous-like material. Although there was a well-defined capsule posteriorly, this tumor invaded the uterine canal anteriorly, as a button-like, firm, sessile polyp.

Microscopically the tumors in the fundus were typical fibromyomas. The small tumor, that had become submucous, was devoid of a capsule on its mucosal margin (see Fig. 7). It was partially degenerated; there were areas of hyaline change and some of liquefaction. In places one recognized the classical architecture of a fibromyoma but, for the most part, typical cell bundles were absent. The tumor contained many arteries (see Fig. 8), i.e., large ones, small ones, and some that were minute. In some areas the stromal cells were arranged loosely; in others they were compact (see Fig. 8). Some of the arteries had extremely thick walls and about them there was a suggestion of periarterial collars of tumor tissue. The stromal cells were essentially uniform in size; there were no mitoses.

The patient is well.

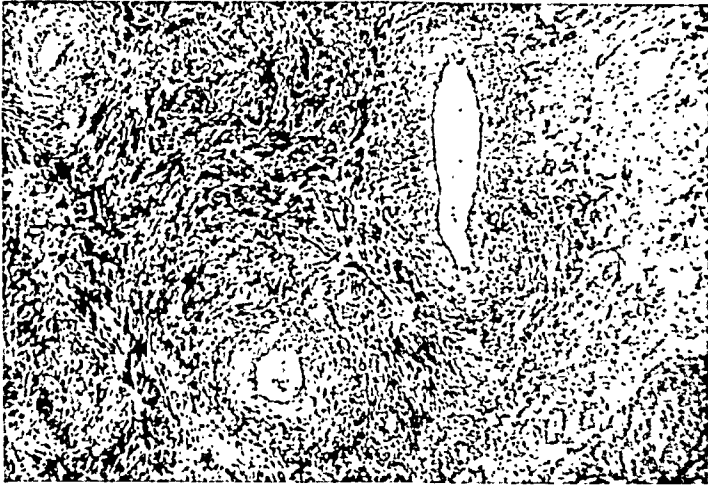


Fig. 8.—(Tumor 3.) The tumor contains many arteries. In some areas the stromal cells are arranged loosely ($\times 52$). (Photographed by Clarence B. Mitchell.)

DISCUSSION

It has been difficult to determine the nature of these tumors, and a careful survey of the literature has not helped materially in their classification. Furthermore there has been a lack of unanimity in the diagnoses suggested by others who have seen these sections. The most frequent reaction is to classify them as unusually vascular fibromyomas. Some believe that they are sarcomas; others consider them hemangiomas.

Although they are more vascular and more cellular than usual, for the following reasons these tumors are classified as fibromyomas: First, a fibromyoma is the most common solid uterine tumor; second, typical fibromyomas were also present in two of the three uteri; third, on gross examination, they appeared to be partially degenerated fibromyomas; fourth, a characteristic feature of their microscopic appearance is the paucity, but not complete absence, of usual fibromyoma architecture (each tumor contains some whorls of muscle fibers with bands of cells cut transversely, longitudinally and obliquely; Tumor 3 most closely approaches the usual microscopic appearance of a fibromyoma); fifth, one is accustomed to think of uterine fibromyomas as relatively avas-

TUMOR 3.—A 41-year-old nullipara was admitted to the Gynecologic Service at Passavant on Jan. 8, 1939; her complaints included lower abdominal pain and irregular, profuse menses. The uterus contained fibromyomas and extended three fingerbreadths above the symphysis. A subtotal hysterectomy was performed. Fig. 7 is a drawing of the opened gross specimen. Attention is directed to the $1\frac{1}{2}$ inch tumor in the posterior wall of the uterus; it was chiefly intramural but bulged into the uterine cavity (see *A* on Fig. 7) at the level of the internal os. Grossly



Fig. 6.—(Tumor 2.) In places the stroma is compact, elsewhere it is loose ($\times 70$). (Photographed by Clarence B. Mitchell.)

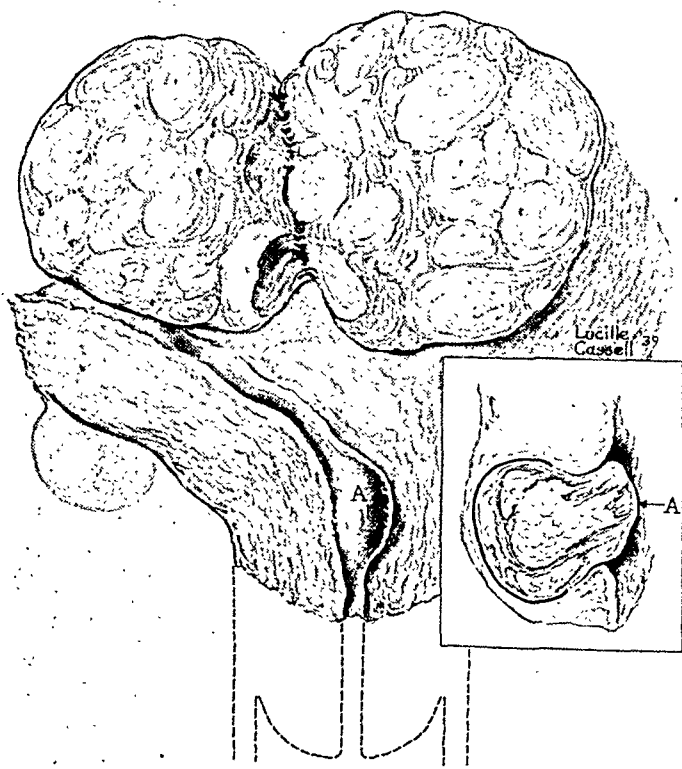


Fig. 7.—(Tumor 3.) Drawing of the opened gross specimen; the uterus had been amputated through the cervix. The tumors in the fundus were typical fibromyomas. At "*A*," a firm sessile intramural tumor bulged anteriorly into the canal, near the internal os. The insert is a vertical section of this tumor. Note the streaks of degeneration in it. Note, also, the capsule only over its posterior aspect. (Photographed by Clarence B. Mitchell.)

changes in a fibromyoma. The task is simplified when the tumor is soft, brainlike, partly necrotic and partly hemorrhagic and contains classical microscopic evidence such as abnormal mesoblastic cells, polymorphism, hyperchromatism and mitotic figures; giant cells are not uncommon. Variations in the histologic criteria, for the diagnosis of sarcoma arising in a uterine fibromyoma, are undoubtedly responsible for the discrepancies which have occurred in the incidence of sarcoma reported by different clinics.

The periarterial collars of tumor cells, so conspicuous in Tumor 1 (see Figs. 1 and 2), suggest that perithelioma might be an appropriate diagnosis. The term perithelioma is not generally accepted today, although it is permissible to speak of a peritheliomatous distribution of tumor cells. MacCallum has expressed the attitude of most pathologists as follows: ". . . there often occurs what seems to be a local necrosis of the tumor cells from lack of sufficient blood supply. This leads to a curious condition in which only those cells which are close to the blood vessels remain alive. . . . Consequently the tumor appears to be made up of blood vessels each with a thick mantle of cells, and such tumors have been described as a separate type under the name angiosarcoma. The cells about the blood vessels have been regarded as arising from a hypothetical tissue spoken of as perithelium, and the tumor, therefore, called a perithelial angiosarcoma. It is possible that tumors with this structure really exist to which the explanation just given will not apply, but I have not seen them."

Tumor 1 appears to be lobulated (see Fig. 1). Each unit consists of an artery surrounded by a wide zone of tumor cells. Individual lobules are demarcated by a zone of necrosis (see Fig. 2). This tumor's structure coincides with MacCallum's description; consequently the terms perithelioma and angiosarcoma can be eliminated from further consideration.

One might think that these tumors are hemangiomas in uterine fibroids. Hemangiomas of the uterus are rare; they have been reported in the literature under the titles of angiomyoma, angiofibroma, hemangioma, hemangiomyofibroma, telangiectatic fibromyoma and hemangiectatic myoma. No illustrations have been found that are identical with the tumors which I have described; however, those which most closely resemble these specimens appear in the reports of angiomas of the uterus.

By definition, a hemangioma is a tumor composed of blood channels; these channels may be dilated capillaries, as in a telangiectasis, or large irregular blood spaces, as in a cavernous hemangioma. There may be proliferation of the intima lining the blood channels. Furthermore, one is likely to think of hemangiomas as tumors of veins although arteries too may participate. Grossly, a hemangioma is a bloody, purple red, vascular tumor; the specimens which I have described were pale, white, and partially degenerated. Furthermore, the blood vessels in these tumors are well-developed arteries of various sizes (not dilated capillaries and blood spaces); most of the arteries possess a delicate intimal lining and a thick muscular media. Consequently these tumors are not true hemangiomas.

cular tumors although it is recognized that there may be great variations in the number, and the size, of their intrinsic vessels. Consequently the ensuing discussion is an interpretation of the unusual microscopic picture found in these fibromyomas.

Each tumor contains areas of degeneration, either focal necrosis, small hemorrhagic zones, edema, liquefaction or hyaline changes. Consequently their vascularity and tendency to a compact stroma (see Fig. 8) may be relative, the result of compression and close packing of tissues; blood vessels and supporting fibrous tissue stroma might persist after intervening bands of smooth muscle fibers had degenerated and disappeared. I doubt that this is the sole explanation for their vascularity because the vessels are larger and more numerous than one usually finds in a fibromyoma, irrespective of its size, location, and the amount of degeneration in it.

The vascularity of a tumor would be altered if there had been interference with its blood supply, e.g., torsion of the pedicle. Neither one of the polypoid tumors was engorged or bloody; they were pale and edematous. Their vessels are normal arteries (see Fig. 5), not distended veins.

In the literature one finds comments on the increased vascularity sometimes encountered in the dependent portions of submucous fibroids. In the specimens under consideration, the increase in arteries is a diffuse phenomenon; it is not restricted to one portion of the tumors.

Sampson's observations on injected uteri are an excellent source of information about the great variations which may occur in the intrinsic vessels of uterine fibromyomas. He found that the vascularity of myomas differs markedly from that of the myometrium; frequently the tumors have more arterial supply but always fewer veins than the uterine musculature in which they are located. In some of his tumors there was extensive development of the intrinsic blood vessels, filled with the arterial injection mass, so that the injected specimen grossly appeared more like "an arterial angioma rather than a myoma." Sampson did not include either microscopic descriptions or photomicrographs in his contributions.

There are facts to support the contention that these tumors had already become sarcomatous, e.g., first, none of them is well encapsulated although in Tumor 3 a capsule is lacking only on the mucosal surface (see Fig. 7), and a capsule would not be expected around polypoid submucous fibroids; second, there is a richly cellular stroma in certain areas of Tumors 2 and 3; third, a few mitotic figures are present in Tumors 1 and 2 (more than an occasional mitosis is needed for the diagnosis of sarcoma. These mitoses are significant. They denote a tendency to rapid growth of tissue); fourth, the St. Luke's patient eventually died of sarcoma. However, there was a long interval, four and one-half years, between the vaginal removal of Tumor 1 and the hysterectomy, when sarcoma was found in the uterus.

Sarcomas are vascular tumors, but it is not typical for them to contain innumerable large normally developed arteries. Great difficulty may be encountered in making the microscopic diagnosis of sarcomatous

Surg. Gynec. Obst. 14: 215, 1912; 16: 144, 1913. (25) *Schumann, E. A.*: Other Tumors of the Uterus, Curtis' Obstetrics and Gynecology, 2: Philadelphia, 1933, W. B. Saunders Co. (26) *Veit-Stoeckel*: Handbuch der Gynäkologie, 6: Part 1, München, 1930, J. F. Bergmann. (27) *Watson, B. P.*: Am. J. Obst. 69: 806, 1914. (28) *Wright, F. W.*: Surg. Gynec. Obst. 43: 282, 1926.

700 NORTH MICHIGAN AVENUE

DISCUSSION

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—As long ago as 1911 I published, with the late Dr. A. H. F. Barbour, two cases of what we then called perithelioma, one of the uterus and one of the tube. As Dr. Gardner has said, this term, perithelioma, is no longer admissible, but the tumors as then described were very similar in gross and in microscopic appearance to those presented today.

Dr. Gardner was so good as to send me the original microscopic preparations from his cases. I was so struck by them that I asked Dr. Arthur Purdy Stout, head of the Surgical Pathological Laboratory of the Columbia University College of Physicians and Surgeons, to go over them with me. I should like to quote Dr. Stout's commentary:

"I have spent some time studying the tumor of the uterus sent to you by Dr. George H. Gardner, which he proposes to call 'Fibromyoma angiomatosum.' It is a most interesting lesion, and I think that we can get some clue to its origin from the section No. 3072 of the original growth which presented in the external os and was removed by cutting its pedicle in 1931. This tumor resembles in many respects a tumor which grows in the skin and subcutaneous tissue, coming from the smooth muscle of the blood vessels. There are other smooth muscle tumors in the skin which come from the hair muscles and the muscles of the genital zones, such as the nipple, areola, and vulva. These are composed exclusively of smooth muscle, but the ones that come from the vessels are also well supplied with large, thick-walled vessels not unlike the ones in the cervical tumor. I think, therefore, that I would call this original tumor a leiomyoma of vascular type. I think that Dr. Gardner is in error in calling the vessels arteries. Just because a vessel has thick muscle walls does not necessarily make it an artery. Differential stains should be done to show the actual distribution of smooth muscle, elastic tissue and connective tissue in order to determine the nature of these vessels. To me they seem much more like thick-walled veins.

"I think that he is probably right in believing that the malignant portion of the growth is a leiomyosarcoma, but it is a great pity not to attempt to get confirmation of this by differential stains. It is of very great interest to find that the tumor, even in its malignant manifestations, still continues to form large vessels."

Dr. Stout has made a special study of these leiomyomas which originate in the smooth muscle of blood vessel walls and tend to occur in the subcutaneous tissues in various regions of the body. He is inclined to think that the tumors described by Dr. Gardner are of essentially the same nature. On the other hand we have always been inclined to think that fibromyomas of the uterus are avascular tumors. As Dr. Stout says in his criticism, the thick-walled vessels are not necessarily arteries, most of them are veins.

After seeing Dr. Gardner's specimens I took at random a number of sections of ordinary fibroid tumors of the uterus to see what type of blood vessels they contained and was rather surprised to find that a great many of those ordinary fibroids had large vessels very much the same as those which Dr. Gardner found in his tumor. It seems entirely possible that the tumor described by Dr. Gardner took origin in the smooth muscle of such vessel walls.

Dr. Stout's suggestion that the tumor be classed as a leiomyoma of vascular type seems to me to fit the picture better than the name suggested by Dr. Gardner. I feel certain, now that attention has been drawn to this tumor, that many more will be described and that agreement will be reached regarding its proper classification.

The important thing clinically is a recognition of the fact that sarcomatous change is a very definite possibility and that, as Dr. Gardner states, avulsion of those growths, when presenting at the cervix, or their removal from the uterine wall by myomectomy is not sufficient; a hysterectomy ought to be done.

A quotation from the Chapter on Angioma in Ewing's *Neoplastic Diseases* supplies a term which would distinguish these tumors from other fibromyomas. "Excessive development of blood vessels occurs in many tumors. . . . Very often such vessels present a normal or nearly normal structure and do not exhibit neoplastic growth. Such tumors are not true angiomas, but their vascularity may be indicated by the term 'angiomatosum.'" An abundance of normally developed arteries (see Fig. 5) constitutes the most striking microscopic characteristic of the tumors which I have described. Consequently fibromyoma angiomatosum is an appropriate name for them.

SUMMARY

An interpretation has been presented for the unusual histologic structure encountered in three, similar, uterine tumors. The microscopic findings include (1) innumerable well-formed arteries, (2) paucity of the usual architecture of a fibromyoma, (3) areas of degeneration, and (4) some tendency to compactness of the cellular stroma. These tumors were submucous; two were polypoid; and the other one lacked a capsule on its mucosal surface. A few mitotic figures have been found in two of the tumors. One shows striking periarterial distribution of tumor cells; this patient eventually died of sarcomatosis. The other patients are reported to be well, one and one-half and two and one-half years, respectively, after operation.

CONCLUSIONS

This is an unusual type of uterine fibromyoma. It appears to be potentially malignant; at any rate the patient from whom the first tumor was removed died of sarcomatosis. Myomectomy, alone, does not seem to be adequate treatment; the uterus should be removed. An appropriate name would serve to distinguish this tumor from other fibromyomas; it could be termed a fibromyoma angiomatosum.

REFERENCES

- (1) *Barbour, A. H. F.*: J. Obst. & Gynaec. Brit. Emp. 24: 61, 1913. (2) *Barbour, A. H. F., and Watson, B. P.*: J. Obst. & Gynaec. Brit. Emp. 20: 116, 1911. Idem: Gynecological Diagnosis and Pathology, Edinburgh, 1922, W. Green and Son. (3) *Bell, W. B., and Clarke, H. H.*: J. Obst. & Gynaec. Brit. Emp. 9: 348, 1906. (4) *Brenner, M.*: Zentralbl. f. Gynäk. 58: 129, 1934. (5) *Clark, J. G.*: Bull. Johns Hopkins Hosp. 10: 11, 1899. (6) *Curtis, A. H.*: A Textbook of Gynecology, ed. 3, Philadelphia, 1938, W. B. Saunders Co. (7) *Doran, A. H. G., and Lockyer, C.*: J. Obst. & Gynaec. Brit. Emp. 14: 320, 1908. (8) *Dorland, W. A. N.*: Surg. Gynec. Obst. 23: 576, 1916. (9) *Eisnerth, P.*: Zentralbl. f. allg. Path. u. path. Anat. 41: 196, 1934. (10) *Ewing, J.*: Neoplastic Diseases, ed. 3, Philadelphia, 1928, W. B. Saunders Co. (11) *Frank R. T.*: Gynecological and Obstetrical Pathology, ed. 2, New York, 1931, D. Appleton-Century Co. (12) *Horgan, E.*: Surg. Gynec. Obst. 50: 990, 1930. (13) *Johns, J.*: J. Michigan M. Soc. 32: 504, 1933. (14) *Kelly, H. A., and Cullen, T. S.*: Myomata of the Uterus, Philadelphia, 1909, W. B. Saunders Co. (15) *Kimbrough, R. A.*: AM. J. OBST. & GYNEC. 28: 723, 1934. (16) *Leith, R. F. C.*: J. Obst. & Gynaec. Brit. Emp. 19: 447, 1911. (17) *Lockyer, C.*: Fibroids and Allied Tumours, London, 1918, The Macmillan Co. (18) *MacCallum, W. G.*: A Textbook of Pathology, ed. 6, Philadelphia, 1936, W. B. Saunders Co. (19) *Neumann, H. O.*: Arch. f. Gynäk. 139: 161, 1930. (20) *Novak, E., and Anderson, D. F.*: AM. J. OBST. & GYNEC. 34: 740, 1937. (21) *Orsos, F.*: Zentralbl. f. Gynäk. 58: 122, 1934. (22) *Pusch, L. C.*: AM. J. OBST. & GYNEC. 24: 907, 1932. (23) *Rutten, E.*: Frankfurt. Ztschr. f. Path. 46: 151, 1934. (24) *Sampson, J. A.*:

ENDOMETRIOSIS OF THE LUNGS*

AN EXPERIMENTAL AND CLINICAL STUDY

JOHN E. HOBBS, M.D., AND A. R. BORTNICK, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital and Barnes Hospital)

ENDOMETRIOSIS is such a commonplace disease, and it has been so often and thoroughly discussed we would feel apologetic were it not for the fact that we have a new aspect of the subject for presentation. We shall, therefore, limit our consideration of its development to those points that are relevant to our problem of endometriosis of the lungs.

Rokitansky, in 1860, first described this lesion as an adenomyoma of the uterine wall. V. Recklinghausen renewed interest in the subject in his publications from 1893 to 1896, in which he ascribed the origin of the heterotopic endometrium in the uterine wall to the development of embryonic rests of the Wolffian ducts. In 1896, Cullen made his first contribution to the subject in describing an adenomyoma of the round ligament. He was the first to show that misplaced endometrial tissue in the uterine wall may be the result of direct invasive growth of the endometrium. In 1899, W. W. Russel was the first to describe endometrial tissue in the ovary, the so-called "chocolate cyst." Koch in 1911, Schwarz, Norris and Cassler in 1919, and Cullen in 1920, described endometrial tissue in the ovary; In 1920, Sampson made his original contribution in which he analyzed 23 cases; the total number on record at that time was less than 20. Since then a voluminous literature has sprung up on the subject. The lesion has been found in a diversity of locations including: vulva, perineum, vagina, urinary bladder, uterus, round, broad, and sacrouterine ligaments, tubes, ovaries, rectovaginal septum, intestines, umbilicus, laparotomy scars, lymph nodes (inguinal, and iliac), thigh, and brachioradialis muscle.

Endometrial tissue has been successfully transplanted to numerous organs in laboratory animals, including the anterior chamber of the eye. The theories which have been promulgated to explain the diversity of endometrial transplants are familiar, namely: Congenital theory, mucosal invasion theory (endometrium and endosalpinx), serosal theory, Sampson's tubal regurgitation theory, and metastatic theory.

For several years it has seemed probable that endometrial tissue might become implanted in the lungs.

This suspicion was based on several known facts: (1) Halban and Sampson have demonstrated endometrial tissue in the lumina of veins and lymphatics. We have sections in our laboratory to show this mode of transportation. Additional support to the fact that endometrial tissue is transported in this way is offered by finding endometrium in the inguinal and iliac lymph glands. Several cases of inguinal implants have been described. Taussig has found that about 10 per cent of the cases in which he has done lymph gland resections for cervix uteri cancer will show endometrial tissue in the iliac glands; (2) normal syncytial tissue and chorionepithelioma are transported to the lungs through the blood stream; (3) the

*Read, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Association, The Seigniory Club, Que., June 17 to 19, 1940.

DR. EMIL NOVAK, BALTIMORE, MD.—On the basis of these photomicrographs which Dr. Gardner has shown and the history of the patients, I feel that all three of these cases are sarcomas of the uterus. Both myomas and sarcomas differ very much in the matter of blood supply, as well as in the distribution of lymph vessels. The latter, for example, are sometimes extremely large and numerous. In the benign myoma the blood supply is ordinarily not a very rich one. Little is known as to the etiology of myoma, although most pathologists feel that the origin is from certain so-called indifferent cells, rather than from the fully formed, mature, involuntary muscle cells of the uterus.

Many of you will remember the term "recurrent myoma" of the uterus, which was not infrequently found in the older literature. It referred to a group of tumors, histologically apparently benign, which recurred after removal. For example, in such a case reported some years ago from Halban's Clinic, a complete operation was done for a myoma which histologically was benign. Several recurrences necessitated repeated operation, and it was only after the last operation that sarcoma was demonstrated microscopically. It must, however, have been present in potential form long before this.

While the finding of mitoses is of great importance in the diagnosis of sarcoma, one frequently finds in cases of undoubted sarcoma many areas in which there is no mitosis whatsoever. In some sarcomas, there is a tendency to the perivascular arrangement of the sarcoma cells, constituting the type spoken of as angiosarcoma. However, this appearance is often due to the fact that the extensive degeneration which involves most parts of the tumor spares the cells immediately around the blood vessels.

Finally, one of Dr. Gardner's cases illustrates the fact that when one finds large, bulky, friable polypoid growths of the endometrium or cervical mucosa one should always suspect the existence of sarcoma. Sarcoma originating in the uterine mucosa always has a tendency to assume this polypoid form, although there is also extensive invasion of the entire uterine wall.

DR. GARDNER (closing).—I think it has been proved that the vessels in these tumors are arteries. In differential stains the relative amount of smooth muscle tissue and connective tissue varies a great deal. Some of the vessels possess these tissues in equal amounts; however in most of them the smooth muscle fibers predominate, a ratio of three or four to one. These vessels are composed of a delicate intima, a thick muscular media and a fibrous tissue adventitia. Furthermore, many have both an external and an internal elastic membrane although in some vessels in the first tumor, the elastic tissue is a very delicate structure.

In several respects these tumors differ strikingly from those described by Dr. Stout. In his leiomyomas of vascular origin arising in the skin, none of the vessels possessed an internal elastic membrane. Furthermore, in many places Dr. Stout found continuity between the smooth muscle fibers of the vessel wall and the tumor itself. Differential stains show that there is a well-defined connective tissue adventitia between the smooth muscle fibers of the vessels and the stroma of the tumors which I have described.

I can understand Dr. Novak's attitude, viz., that these tumors might be sarcomas. I have cited the observations which led me to classify them as benign tumors, although they appear to be potentially malignant.

The accompanying photomicrographs, Figs. 1 to 6 inclusive, give a visual picture of the development of the pulmonary implants.

With this phase completed, the next problem attempted was to impregnate some of the animals which had been previously given endometrial implants in the lungs to see if a decidual reaction would occur. In pregnant women, ectopic endometrial tissue may undergo decidual



Fig. 1.—The endometrial tissue has proliferated and almost obliterated the lumen of the vein.

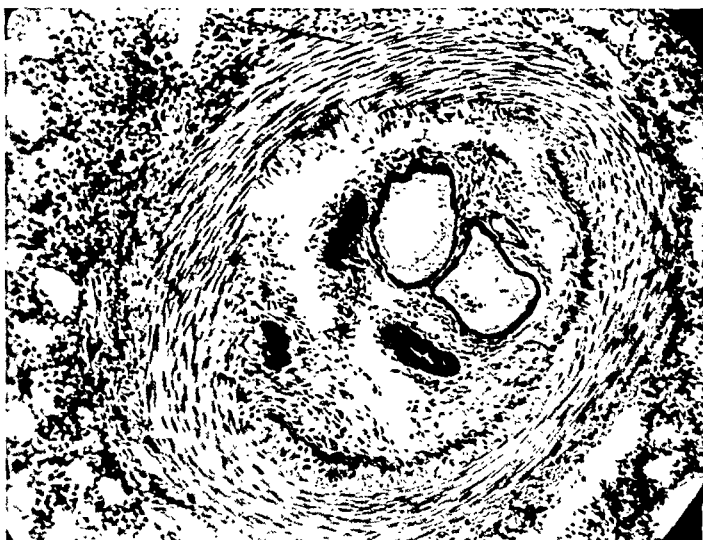


Fig. 2.—The lumen of an artery has been obliterated.

formation. Several years ago Loeb proved, and his work has been confirmed, that if the horn of a guinea pig or rabbit is tied off and the animal becomes pregnant, a decidual reaction will not occur in the sterile horn unless the mucosa is traumatized in some manner such as incising, passing of a suture, etc. Therefore, it was with some misgiving that we undertook this experiment.

only plausible explanation for finding endometrial tissue in such locations as the brachioradialis muscle (Navratil and Kramer) and thigh (Mankin) is that it must get into the systemic circulation; and (4) the diversity of tissues in which endometrial implants have been found would indicate the lungs are not resistant to its growth. In an attempt to confirm this suspicion, with the encouragement of our Chief, Dr. Otto H. Schwarz, we decided to do some experimentation.

METHOD

Obviously, our first problem was to implant the endometrium of a laboratory animal into the lungs and to note whether it would grow. We realized the use of large rabbits (2,000 Gm. or over) would be advantageous for two reasons. In the first place, the uterus and horns are quite large, facilitating the removal of the mucosa; and in the second place, we conceived the idea of injecting the tissue into the ear vein, a very simple procedure. We could thereby simulate the transportation of tissue through the uterine veins and also be assured of wide dissemination of the tissue throughout the lungs. Our mortality dropped to zero when we stopped doing hysterectomies and only did hysterotomies for removal of the mucosal clippings. The horn was closed with a running suture of silk. Very little trauma and no shock attended this procedure. In the last 15 operations with improved technique, only one animal died as a direct result of the operation, and this was attributed to the anesthesia.

Previous to the operation theelin in oil was given in order to stimulate growth of the endometrium and thereby facilitate the removal of the tissue. The clippings suspended in normal saline were injected into the ear vein through an 18 gauge needle. After the injection the vein was thoroughly washed with normal saline solution. It was astonishing what large pieces of mucosa could be injected without being fatal to the animal.

Table I shows a résumé of this experiment.

TABLE I. ENDOMETRIOSIS OF LUNGS

RABBIT	THEELIN (2,000 U.)	ENDO- METRIUM IMPLANTED	KILLED	DIED	ENDOMETRIUM IN LUNGS
1980	1/22/38	1/24/38	4/16/38		None
1981	1/22/38	1/24/38	4/16/38		Stroma
1944	1/28/38	1/31/38		3/22/38	Stroma (?) and frag- mented epithelium (?)
A-6	2/ 4/38	2/ 7/38	4/16/38		None
A-7	2/ 8/38	2/10/38		3/15/38	Glands
A-8	2/12/38	2/15/38		3/ 8/38	None
A-9	2/12/38	2/15/38		3/ 6/38	Stroma and glands
A-10	2/20/38	2/23/38		4/ 2/38	Glands
A-19	2/20/38	2/23/38		4/ 4/38	"Chocolate cyst," stroma and glands
A-23	2/26/38	2/28/38		4/15/38	Glands
A-537	11/26/39	11/27/39	4/30/40		Stroma and glands
A-538	11/26/39	11/27/39	4/30/40		None

Summary: Out of 12 rabbits operated, 8 showed endometrial implants.

Control: The lungs of 10 normal rabbits were examined for endometrial tissue and none was demonstrated.

TABLE II. ENDOMETRIOSIS OF LUNGS PLUS PREGNANCY

RABBIT	THEELIN (2,000 U.)	ENDO- METRIUM IMPLANTED	BRED	KILLED	DIED	RESULTS
A-305	7/17/39	7/19/39	8/27/39	9/20/39		Uterus: Pregnant both horns Lungs: Diffuse glands and decidua
A-307	7/24/39	7/26/39	9/19/39	10/11/39		Uterus: Pregnant, unoperated horn Lungs: Glands and decidua
A-308	7/24/39	7/26/39	10/ 8/39	10/30/39		Uterus: Pregnant, unoperated horn Lungs: Glands and decidua
A-545	11/30/39	12/ 1/39	1/30/40		2/12/40	Uterus: Enlarged and succulent, decidua? Lungs: Glands, no decidua. Mis- carriage?
A-546	11/30/39	12/ 1/39	1/30/40	2/23/40		Uterus: No evidence of pregnancy Lungs: Glands, decidua?
A-592	12/14/39	12/18/39	1/30/40	2/23/40		Uterus: Pregnant both horns Lungs: Glands and decidua

Control: The lungs of 10 normally pregnant rabbits were examined for trophoblast or decidua and none was found.

TABLE III. ENDOMETRIOSIS OF LUNGS PLUS STILBESTROL

RABBIT	THEELIN (2,000 U.)	ENDO- METRIUM IMPLANTED	DIED	KILLED	STIL- BESTROL	RESULTS
A-539	11/26/39	11/29/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Endo- metrium thin
A-540	11/26/39	11/29/39		4/30/40	Given*	Lungs: One small area of stroma in blood vessel Uterus: Endometrium very thin
A-547	11/30/39	12/ 1/39	12/ 1/39	Anes- thesia		
A-589	12/14/39	12/18/39	3/23/40		Given*	Lungs: Diffuse endo- metriosis Uterus: Endometrium thin, very few glands
A-590	12/14/39	12/18/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Necrotic, no epithelium
A-591	12/14/39	12/18/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Necrosis of endometrium and myometrium

Control: Animals reported in Table I serve as controls.

*Rabbits were given 1 mg. of stilbestrol 3 times a week from 1/30/40 to 4/16/40 (77 days); then 2 mg. 3 times a week for 7 days, and finally, 5 mg. daily for 5 days. All received a total of 64 mg., except No. A-589, which received 22 mg.

Table II gives a composite picture of this experiment.

The photomicrographs, Figs. 7 to 9 inclusive, demonstrate unequivocally the development of a decidual reaction in the lung implants. The trauma, if present, that was necessary to produce the decidual reaction in the pulmonary implants was problematical.



Fig. 3.—The wall of this vein has been disrupted in two places.



Fig. 4.—Only a fragment of the vein wall remains. The endometrial tissue is invading the parenchyma of the lung.

The next problem attacked was to demonstrate the effect of an estrogenic hormone on the implanted tissue. One should expect hyperplastic changes in both the glands and stroma with prolonged administration of this hormone in large doses. Table III presents the data on this experiment.

turn inhibits or diminishes ovarian activity, so that there is a lack of estrone stimulation to the endometrium. We are making further experiments to demonstrate the effect of estrogenic hormones in graduated doses on normal and aberrant endometrial tissue.

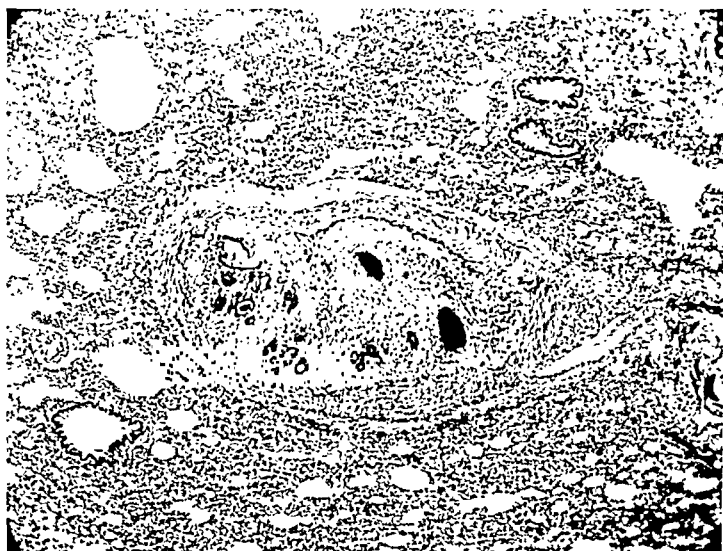


Fig. 7.—The endometrial stroma in this vein has undergone decidual formation.

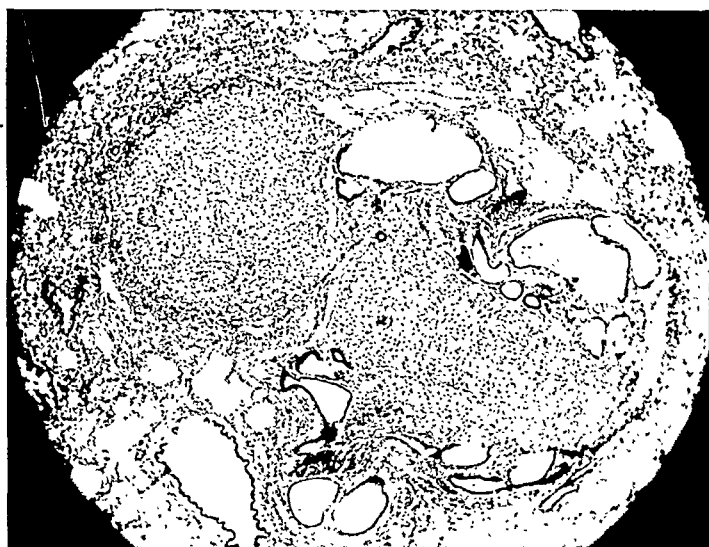


Fig. 8.—A diffuse decidual reaction.

We believe this work is not only of didactic interest but is of considerable practical importance. The theoretical possibilities are obvious. We have attempted to demonstrate some of these possibilities in fact.

DISCUSSION

In the first place, we are of the opinion that vicarious menstruation is due to an endometrial transplant in whatever region from which the

The photomicrograph, Fig. 10, demonstrates the effectiveness of stilbestrol* in this experiment. It is especially interesting to note that Rabbit A-589, which had about one-third the total dosage administered in a little over one-half the time, showed diffuse endometriosis of the lungs complicated by empyema from which it apparently died. Those

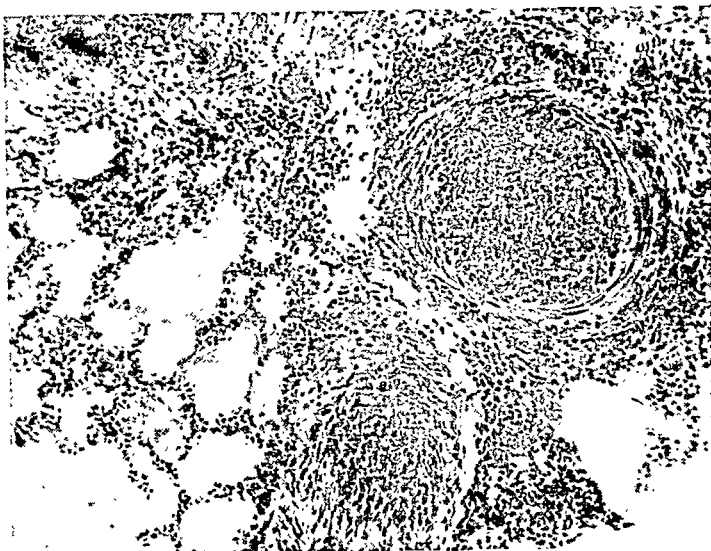


Fig. 5.—Two veins filled with endometrial stroma.



Fig. 6.—A microscopic section through the cyst wall showing typical endometrial tissue.

receiving larger doses over a longer period of time showed very little or no endometrial tissue in the lungs. Also the uteri showed inactive mucosae and necrosis in some cases. It is a known fact that excessive doses of stilbestrol will produce necrosis of the rabbit's uterus. It may be possible that large doses suppress the anterior pituitary which in

*We wish to express our appreciation to Eli Lilly and Company, Indianapolis, Indiana, for the generous supply of stilbestrol and for their interest in this experimental work.

the hemoptysis recurred for a few months and has not returned now for over two and one-half years. The other two patients have histories and physical signs characteristic of pelvic endometriosis. Each has hemoptysis at the menstrual period. The fact that the hemoptysis occurred simultaneously with the development of the pelvic endometriosis, is suggestive of an endometrial implant in the lungs.

Another practical consideration is that of tumor formation in the lungs. This may be a source of some of the primary benign and malignant tumors in the lungs of women. Our experiments have demonstrated that the aberrant endometrium may be localized or grow in a diffuse manner. Misplaced endometrial tissue has the same potentiality of malignant development as has normal endometrium. In fact, it possesses two characteristics of malignant cells. First, it is invasive, and second, it will live and proliferate in a foreign host. Statements are made that it is rare for ectopic endometrium to become malignant.



Fig. 11.—Papillary growth of endometrium in the lung.

We wonder whether that statement is correct. Can it be that this tissue is not always recognized as a result of changes in morphology and location? It would seem that this tissue has a greater potentiality for malignant development by virtue of the fact that it has the "growth urge" even in an alien tissue. It is well known that some adenocarcinomas of the ovaries arise from endometrial implants. The papillary serous cystadenomas may arise from the same source. Fig. 11 shows a papillary growth of this tissue in the lung. Added evidence to support this theory that papillary serous cystadenomas arise from Müllerian derivatives can be demonstrated in the human ovary. We have sections in our laboratory to show the development of the germinal epithelium of the ovary into tissue that morphologically simulates endometrial tissue. In many areas this tissue grows in a papillary formation. Through the courtesy of Dr. Evarts A. Graham, we have had the opportunity

periodic discharge issues. These implants may reach the systemic circulation either through a patent foramen ovale or propagate through the capillaries of the lungs and reach the left heart. How else could such tissue reach the arm and thigh? With this possibility in mind, we have made every effort to obtain tissue from women having vicarious menstruation, but to date have not succeeded. We have observed three women



Fig. 9.—A high-power photomicrograph of a portion of Fig. 8, showing characteristic decidual cells and epithelial plasmodia.



Fig. 10.—A low-power photomicrograph through the lung of A-589, showing widespread gland and stromal proliferation.

who have or have had vicarious menstruation, and although we have not been able to demonstrate ectopic endometrium in the area from which the blood came, the history and physical findings are presumptuous.

The first patient showed endometriosis of the inguinal lymph nodes and hemoptysis at each menstrual period. The hemoptysis stopped following deep x-ray therapy to the ovaries. After five months

DISCUSSION

DR. ROBERT A. KIMBROUGH, JR., PHILADELPHIA, PA.—We have seen from Dr. Hobbs' slides that there is certainly histologic identification of the implants with endometriosis, and we must concede that he has been successful in transplanting endometrial tissue into the lung. Since Dr. Sampson demonstrated the presence of endometrial fragments in the venous sinuses of the uterus as long as eighteen years ago, it is perhaps surprising that so few instances of distant metastasis have been observed.

I would like therefore, to cite the following case as a possible example of endometriosis of the lung: Mrs. S. J., aged 43 years, para ii, consulted me on March 11, 1940 because of severe pain in the right posterior lower chest occurring synchronously with her two previous menstrual periods. On each occasion the pain was of three days' duration, and at the last period the pain was severe enough to require morphine for relief. Respiratory movements did not affect the intensity of the pain, and there was no hemoptysis or cough. In the intervals between these attacks she had had no discomfort whatsoever.

General physical examination revealed nothing of importance. There were no unusual auscultatory findings in the chest, and the pelvic organs were normal except for the presence of a small intramural uterine myoma. An x-ray study of the chest revealed nothing abnormal, and in particular no shadow over the area affected by the pain. Despite this negative study a tentative diagnosis of endometriosis of the lung was made and further observation was advised.

Unfortunately the patient's subsequent course has weakened my original opinion. She had one more attack of pain four or five days subsequent to her next period, and has recently had two menstrual periods attended by no recurrence of discomfort. Is it not possible, however, that three successive menstrual reactions in this heterotopic endometrium may have either temporarily or permanently destroyed its functional ability?

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Hobbs has clearly established the fact that endometrial tissue will grow in the lung, and that such ectopic tissue exhibits the same physiologic responsiveness as does the normal uterine mucosa. The important question is the applicability of this work to the general problem of the histogenesis of endometriosis.

In our own laboratory we have often seen emboli of endometrium in the veins and lymphatics, but there are few who accept Halban's theory of the lymphogenic etiology of pelvic endometriosis. The distribution of endometrium in the latter condition is not at all what would be expected if the lymphatic route of the dissemination were the important one.

In another section of his work Dr. Hobbs shows that his studies may possibly be applied to the explanation of vicarious menstruation, but on this point, as he himself states, the evidence is still very incomplete. I am inclined not to agree with him that the presence of actual endometrium is necessary for the occurrence of vicarious menstruation, as I think that such vicarious bleeding is readily explainable on the basis of certain vascular changes, such as increased fragility of the vessels, which have been shown to characterize the menstrual epoch. Furthermore, the recent studies of Collip and others have shown marked hyperemia of certain areas of the nasal mucosa in monkeys at the time of menstruation, and the frequent cases of vicarious nasal menstruation in women would seem to indicate that such vascular changes are probably sufficient to explain this phenomenon.

It would seem incredible that actual endometrial tissue is present in all cases of vicarious menstruation. For example, in a recent patient, in addition to nasal and rectal vicarious menstruation, large purple purpuric areas appeared on the lower extremities below the knee. While, therefore, Dr. Hobbs is to be complimented on his project of searching for endometrium in these cases of vicarious menstruation, I would be inclined to think that this search will not be successful.

to make a microscopic study of 33 primary lung tumors removed from women. We were not able to demonstrate endometrial tissue in any of these cases.

Finally, if endometrial tissue does occur in the lungs, it is conceivable that hemoptysis and roentgenograms may lead one to suspect tuberculosis. In many cases of suspected tuberculosis, tubercle bacilli cannot be demonstrated. It seems quite likely that a diffuse or circumscribed lesion in the lungs would produce a picture that might be mistaken for tuberculosis. We urge the roentgenologist, internist, and chest surgeon to keep this possibility in mind.

The fact that the lesion has not been demonstrated in the lungs does not necessarily mean that it does not exist nor that it is not frequent. For example, endometriosis of the pelvis was not recognized with any frequency until Sampson's report in 1920. Now we know the lesion is present in about 10 per cent of adult women. Banting and Best called attention to the lesion of the islands of Langerhans in diabetes mellitus. The lesion has always been there, but it was not recognized. Many other examples showing the fallacy of the argument that because a lesion has not been found it does not exist, might be enumerated.

CONCLUSIONS

1. Endometrial tissue can be transported through veins.
2. Endometrium of the rabbit can be transported through the veins to the lungs where it will remain viable and invade the parenchyma.
3. Implants of uterine and horn mucosa in the lungs may undergo decidual formation if the animal becomes pregnant.
4. An estrogenic hormone (stilbestrol) in relatively large doses apparently stimulates the endometrial tissue implanted in the lungs. Excessively large doses may inhibit the growth of this tissue.
5. Clinical evidence correlated with experimental work leads us to the following deductions:
 - a. Vicarious menstruation is a result of an endometrial implant in whatever region from which the periodic bloody discharge issues.
 - b. Certain benign and malignant tumors in the lungs of women may arise from endometrial transplants.
 - c. Pulmonary endometrial implants may be mistaken for tuberculosis.

REFERENCES

- (1) Halban, J.: Wien. klin. Wchnschr. 37: 1205, 1924. (2) Hobbs, John E., and Bortnick, A. E.: Surg. Gynec. Obst. 69: 577, 1939. (3) Jacobson, V. C.: Arch. Surg. 5: 281, 1922. (4) Loeb, L.: Proc. Soc. Exper. Biol. & Med. 1: 93, 1903-1907. (5) *Idem*: Proc. Soc. Exper. Biol. & Med. 5: 102, 1907-1909. (6) *Idem*: J. A. M. A. 50: 1897, 1908. (7) Mankin, Z. W.: Arch. f. Gynäk. 159: 671, 1935. (8) Navratil, E., and Kramer, A.: Klin. Wchnschr. 15: 1765, 1936. (9) Sampson, J. A.: AM. J. OBST. & GYNEC. 14: 422, 1927. (10) *Idem*: Am. J. Path. 3: 93, 1927. (11) Seelig, M. G., and Hobbs, John E.: Festschrift dedicated to Robert Tilden Frank, June, 1937, St. Louis, The C. V. Mosby Company, 1937. (12) Taussig, F. J.: AM. J. OBST. & GYNEC. 36: 819, 1938.

VITAMIN K IN OBSTETRICS*

A REVIEW OF ONE YEAR'S EXPERIENCE

L. M. HELLMAN, M.D., L. B. SHETTLES, PH.D., AND N. J. EASTMAN, M.D.,
BALTIMORE, MD.

(From the Department of Obstetrics, The Johns Hopkins University and Hospital)

IT IS well known that the newborn infant exhibits an especial tendency to bleed. For example, the incidence of retinal hemorrhage during the first week of life ranges between 12 and 30 per cent,^{1, 2} while bloody spinal fluid is demonstrable in one baby in ten at this period.³ It is equally well known that this hemorrhagic tendency sometimes assumes pathologic proportions and gives rise not only to the syndrome of hemorrhagic disease, but in conjunction with trauma or anoxia, to cerebral bleeding, possibly the most common cause of neonatal death.

A rational explanation for this tendency of the newborn to bleed was advanced in 1937 by Brinkhous, Smith, and Warner,⁴ who showed that the plasma prothrombin level of babies at birth is exceedingly low, ranging from 14 to 39 per cent of the usual adult value. These observations were subsequently confirmed by Moore and Javert,⁵ as well as by Hellman and Shettles⁶ in our clinic; the latter authors added the information that the plasma prothrombin concentrations of premature infants are extraordinarily low, averaging but 11 per cent of the adult figure. Of particular import is the fact that each of these groups of workers (Brinkhous, Smith, and Warner; Moore and Javert; Hellman and Shettles) included in their report a case of hemorrhagic disease, and in every instance the prothrombin level was the lowest encountered, namely, about 5 per cent of the adult value. Since authorities agree that plasma prothrombin is essential for clot formation and is, in all probability, the determining factor in the rate of blood coagulation, these observations place the etiology of hemorrhagic diatheses in the newborn on an intelligible basis.

From a practical viewpoint, of course, the importance of these findings hinged on the discovery of some substance capable of raising the low prothrombin levels of these infants, a need which was met by the discovery of Vitamin K by Dam in 1935, and its subsequent purification and synthesis by Almquist and Stoksted, Doisy and his associates, Fieser and his co-workers, Ansbacher, and a score of other investigators. Vitamin K is a fat-soluble substance, the absence of which in the diet of chickens causes the blood to become very slow in clotting, with the result that multiple hemorrhages develop; indeed, the blood from chickens fed on a vitamin K deficient diet will stand in the laboratory over night without clotting. Upon studying this blood, investigators have found that its poor clotting properties are ascribable to the fact that the normal amount of prothrombin is lacking. Upon administering vitamin K to such chickens, the plasma prothrombin is promptly raised, the clotting time accelerated, and the hemorrhagic diathesis cured. Vitamin K is

*Presented at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Que., Canada, June 17 to 19, 1940. Read by Dr. N. J. Eastman.

DR. EDWARD ALLEN, CHICAGO, ILL.—With reference to a chocolate cyst in the lung, some years ago we injected large amounts of estrogenic substances into rabbits which previously had had implants of endometrial tissue in the eye. Sufficient hormone was given to produce a metaplasia of the endometrial cells and a change of the connective tissue into cells of typical decidual reaction. In none of these sections did we find any evidence of bleeding.

I would raise the question whether what Dr. Hobbs has described may be called a chocolate cyst in an animal that does not bleed from the endometrium. I would also question the statement that bleeding from the lung may be taken as evidence of ectopic tissue in cases where tuberculosis might be present. Hemoptysis is rather common at the time of the menstrual period in tuberculosis due to increased fragility of blood vessels.

DR. HOBBS (closing).—I think Dr. Novak will have to concede that endometrial tissue may be transported through the lymphatics and through the blood stream into the systemic circulation. How else can he explain the ectopic tissue found in the brachio-radialis muscle and in the thigh? Of course, I do not say that every vicarious menstruation has this basis, but we are hoping to demonstrate ectopic endometrial tissue in women having vicarious menstruation.

TABLE II.* THE PLASMA PROTHROMBIN LEVELS OF MOTHER AND CHILD, EXPRESSED IN DILUTION UNITS, IN TEN FULL-TERM DELIVERIES FOLLOWING TREATMENT OF THE MOTHER DURING LABOR

NAME	INFANT WEIGHT	HOURS FROM ONSET OF TREATMENT TO DELIVERY		PROTHROMBIN DILUTION UNITS		
				MOTHER PRIOR TO TREATMENT	MOTHER AT DELIVERY	INFANT AT DELIVERY
		hr.	min.			
V. P.	3,550	19	59		231.9	148.5
M. Y.	3,310	16	57		272.8	81.2
M. Z.	3,410	14	50		273.7	78.0
E. O.	3,260	12	38	221.0	261.8	72.0
E. M.	3,040	11	43	136.3	162.3	66.6
E. J.	3,080	6	57	173.7	238.3	71.5
R. B.	3,075	6	39	128.7	175.6	70.5
M. B.	3,750	4		253.4	296.0	67.7
L. S.	3,220	1	40	155.8	191.4	53.9
D. C.†	2,875	1	29		116.0	21.6
Average	3,347.8			178.1	233.7	78.7

Dose of vitamin K concentrate, 9,000 units.

*From *Shettles, Delfs and Hellman*: Bull. Johns Hopkins Hosp. 65: 419, 1939.

†Not included in the average. Duration of treatment too short to be effective.

antenatal administration of vitamin K to the mother, the question at once arose as to the practical value of such a procedure. Would it diminish neonatal mortality by eliminating a certain group of hemorrhagic conditions? It was realized, of course, that massive cerebral hemorrhage resulting from severe birth trauma could not be prevented by this measure. However, it is common experience that many infants succumb to cerebral hemorrhage several days after delivery; thus, in Craig's careful pathologic study of 126 neonatal deaths from cerebral hemorrhage,⁸ it was found that the majority of the deaths occurred between the second and sixth day, and some as late as the second and third week. The evidence suggests that in these cases minimal trauma at birth precipitated small hemorrhages which continued to ooze over a number of days; and it would seem conceivable that some of these infants might have been saved had their blood at birth exhibited better clotting properties. So far as outright hemorrhagic disease is concerned (estimated as occurring once in 200 cases), here we would expect the antenatal administration of vitamin K to offer positive prophylaxis.

But these considerations are theoretical only, and in order to test their validity, the following program of study has been carried out. Beginning Sept. 1, 1939, every other patient in labor admitted to the Obstetrical Service of the Johns Hopkins Hospital was given vitamin K by mouth. The preparation used was 2-methyl-1, 4 naphthoquinone, in a single dose of 2 mg.; this synthetic product is known to possess four times the potency of the vitamin K concentrate (vitamin K₁) used by Hellman and Shettles in their prothrombin studies reported in Tables I and II. Preliminary observations, moreover, showed that when this substance is fed to mothers during labor, a smaller dose is necessary to raise the plasma prothrombin of the infant and its action is more rapid. As of May 1, 1940, 384 mothers had received vitamin K in labor, while the alternate control series numbered 392. The two series were similar

found in a wide variety of foods, the richest sources being alfalfa, hog's liver, hemp seed, and decayed fish meal.

If low plasma prothrombin levels in experimental animals can be raised by the administration of vitamin K, it seemed reasonable to hope that similar results could be achieved in the newborn. To this end, work was begun in January of 1939, along two avenues of approach: (a) antenatal administration of vitamin K to the mother and (b) direct administration of vitamin K to the infant after birth. The results of these investigations have been published by Shettles, Delfs, and Hellman⁷ and may be summarized as follows:

1. The plasma prothrombin level of the newborn infant can be raised severalfold by administering vitamin K to the mother antenatally, even when it is given as late as four hours before delivery (Tables I and II).

2. Although the feeding of vitamin K to the baby after birth also increases its prothrombin concentration, the levels so reached are not as high as those achieved by antenatal administration to the mother.

TABLE I.* THE PLASMA PROTHROMBIN LEVELS OF MOTHER AND CHILD, EXPRESSED IN DILUTION UNITS, IN THIRTY-ONE FULL-TERM DELIVERIES

NAME	RACE	INFANT WEIGHT	PROTHROMBIN DILUTION UNITS	
			MOTHER	INFANT
C. B.	W.	3,660	138.9	39.2
Z. B.	C.	2,825	202.9	13.7
R. B.	W.	4,010	201.2	33.8
E. B.†	W.	2,880	92.4	28.2
		2,800		26.8
N. B.	C.	3,305	157.0	41.3
N. B.	C.	3,600	45.0	14.0
M. C.	C.	4,075	99.0	36.5
M. C.	W.	3,120	45.8	14.8
N. E.	W.	3,290	130.6	26.8
B. F.	C.	2,465	237.6	60.4
M. G.	C.	2,535	173.2	32.2
J. G.	W.	3,620	129.8	15.0
E. H.	W.	3,550	124.4	25.6
B. H.	W.	3,800	150.5	28.6
A. I.	W.	2,360	149.9	32.6
E. J.	C.	3,040	151.8	34.4
D. J.	C.	3,000	85.0	14.9
M. J.	W.	3,850	295.4	36.0
R. K.	W.	3,310	129.8	62.5
S. M.	C.	3,180	61.6	21.3
E. R.	W.	3,920	85.8	20.0
E. S.	W.	2,670	123.8	22.4
M. S.	W.	3,110	144.0	34.4
C. S.	C.	2,760	117.0	28.4
B. T.	C.	2,675	46.2	14.2
M. T.	W.	3,700	189.0	33.7
A. W.	C.	2,675	99.8	33.8
P. W.	C.	3,775	79.2	20.5
R. W.	C.	3,010	164.3	26.6
E. W.	C.	2,470	124.4	27.7
G. Z.	W.	3,400	97.4	13.8
Average		3,201.2	131.4	28.6

*From *Shettles, Delfs and Hellman*: Bull. Johns Hopkins Hosp. 65: 419, 1939.

†Double ovum twins.

Since observations on a substantial series of cases had shown that the plasma prothrombin level of the newborn can be raised at will by the

hemorrhage was present, sufficient to account for the death of the baby. Although the hemorrhages in Case 16 were small in degree, their widespread character suggests that they may have been responsible for the death of the baby, in the ab-

TABLE III. INFANT DEATHS AMONG 384 CASES IN WHICH THE MOTHERS RECEIVED VITAMIN K DURING LABOR. UNLESS OTHERWISE STATED NO HEMORRHAGE WAS DEMONSTRABLE AT AUTOPSY

NO.	HIST. NO.	TYPE OF DELIVERY	WEIGHT (GM.)	AGE	AUTOPSY
1	179744	Spontaneous	1,150	7 Hours	Prematurity; atelectasis
2	199012	Low forceps	1,360	2 Days	Prematurity; atelectasis
3	192634	Spontaneous	2,025	Stillborn	Prematurity; atelectasis
4	187349	Spontaneous	2,860	8 Hours	Aspiration gastric contents
5	121085	Rupture of uterus	3,740	Stillborn	Lungs unexpanded
6	121354	Breech extraction	3,980	Stillborn	Hemorrhage, sub-arachnoid

TABLE IV. INFANT DEATHS AMONG THE 392 ALTERNATE, CONTROL CASES IN WHICH THE MOTHERS DID NOT RECEIVE VITAMIN K. UNLESS OTHERWISE STATED, NO HEMORRHAGE WAS PRESENT AT AUTOPSY

NO.	HIST. NO.	TYPE OF DELIVERY	WEIGHT	AGE	AUTOPSY
1	190818	Low forceps	1,145	10 Hours	Prematurity; atelectasis
2	136565	Spontaneous	1,320	2 Days	Pneumonia; hemorrhage, subcapsular of liver; cephal-hematoma
3	187672	Spontaneous	1,390	18 Hours	Prematurity; atelectasis
4	125648	Cesarean section, placenta previa	1,350	19 Hours	Prematurity; hyaline membrane
5	125648	Cesarean section, placenta previa	1,180	6 Hours	Prematurity; atelectasis
6	102128	Cesarean section, pre-eclampsia	1,670	24 Hours	Prematurity; hemorrhage in lungs and thymus
7	121686	Spontaneous	2,375	Stillborn	Atresia of duodenum
8	129796	Spontaneous	1,965	8 Hours	Prematurity; atelectasis
9	190295	Cesarean section, repeat	2,780	2 Days	Hemorrhage, pulmonary
10	193499	Cesarean section, pre-eclampsia	2,000	4 Days	Hemorrhage, pulmonary
11	198014	Spontaneous	3,185	Stillborn	Atelectasis
12	181103	Breech extraction	3,435	3 Days	Hemorrhagic disease
13	185441	Breech extraction	2,970	18 Hours	Hemorrhage, cerebral
14	178584	Version and extraction	2,500	Stillborn	Hemorrhage, cerebral
15	173614	Low forceps	3,160	1 Hour	Hemorrhage, cerebral
16	177143	Spontaneous	3,985	2 Days	Hemorrhages, minute in brain, lungs, spleen, adrenal, thymus, and liver

in every respect, the distribution of patients according to race, parity, contracted pelvis, operative incidence, and premature labors, being approximately the same in the two groups.

It would seem pertinent to inquire first whether any harm can accrue, either to mother or child, from the administration of vitamin K in labor. So far as could be determined, there were no ill effects in this series of 384 cases. The puerperal morbidity was the same in the two groups. Concerning puerperal thrombophlebitis, the incidence of which might conceivably be increased as a result of the raised plasma prothrombin of the mother, there were two cases in the control series and one in the vitamin K group. The question is often asked whether vitamin K affects post-partum hemorrhage. Since blood loss after delivery is controlled by contraction of the uterine muscle fibers and not primarily by blood coagulation, no specific effect would be anticipated; and this supposition was borne out in the present study, the incidence of post-partum hemorrhage and the degree of blood loss at lower levels being approximately the same in the two groups. There were two maternal deaths in the vitamin K series.

The first occurred in a 31-year-old, colored para vii, whose previous 6 infants had been delivered per vaginam without difficulty. She had a contracted pelvis, however, with a diagonal conjugate of 10.5 cm. In the present labor, brow presentation of an eight-pound baby resulted in spontaneous rupture of the uterus, after seventeen hours of labor. Death occurred eleven days after hysterectomy, from subphrenic abscess and pneumonia. The other maternal fatality in the vitamin K series occurred in a normal, twenty-two-year-old, colored primigravida, five minutes after the administration of caudal anesthesia; chemical studies showed that the novocaine had been injected into the spinal canal rather than into the caudal space. It would seem evident that these two deaths were in no way related to the fact that the mother had received vitamin K. In the control series there were no maternal deaths.

Turning now to the newborn, the neonatal course of surviving infants was similar in the two series, the weight at discharge in relation to the birth weight being the same in the two groups. The stillbirth and neonatal mortality figures are as follows: Control series, 16 deaths, or 4.1 per cent mortality; vitamin K series, 6 deaths, or 1.5 per cent mortality. The infant death rate in the control series, accordingly, was 2.7 times that in the vitamin K group. Statistical analysis of these figures shows that they are probably significant; indeed, the chances are 45.6 to 1 against the likelihood that the difference in death rates in the two series was due solely to sampling error.

From a clinical viewpoint, these findings become more significant when the autopsy studies on these infants are reviewed.

As may be seen in Table III, hemorrhage was demonstrable at autopsy in but one of the six fatal cases in the vitamin K group, No. 6; this baby weighed eight and three-fourths pounds, presented by the breech with a hand prolapsed, and died in the course of a difficult breech extraction; autopsy showed subarachnoid hemorrhage. In the control series, hemorrhage into one or another organ was demonstrable in 9 of the 16 autopsies, or in 56 per cent (Table IV). In one instance, Case 12, we were obviously dealing with an outright case of hemorrhagic disease, necropsy revealing extensive hemorrhages in the cerebral vault, lungs, spleen, adrenal, and intestines; plasma studies on this baby before death showed that the prothrombin concentration was too low to be read. In Cases 13, 14, and 15, extensive cerebral

REFERENCES

- (1) *Jacobs, M. W.*: J. A. M. A. 83: 1641, 1924. (2) *Edgerton, A. E.*: Arch. Ophth. 11: 838, 1934. (3) *Sharpe, W., and MacLaire, A. S.*: AM. J. OBST. & GYNEC. 9: 452, 1925. (4) *Brinkhous, K. M., Smith, H. P., and Warner, E. D.*: Am. J. M. Sc. 193: 475, 1937. (5) *Moore, R. A., and Javert, C. T.*: Personal communication. (6) *Hellman, L. M., and Shettles, L. B.*: Bull. Johns Hopkins Hosp. 65: 138, 1939. (7) *Shettles, L. B., Delfs, E., and Hellman, L. M.*: Bull. Johns Hopkins Hosp. 65: 419, 1939. (8) *Craig, W. S.*: Arch. Dis. Childhood 13: 89, 1938.

DISCUSSION

DR. WILLIAM C. MENGERT, Iowa City, Iowa (by invitation).—Hemorrhagic disease of the newborn is now a well-understood entity with a sound therapeutic basis in vitamin K administration. Transfusion of blood, previously the best available treatment, represented a replacement of plasma prothrombin, often raising the level above that necessary to protect from hemorrhage. Even now, however, blood transfusion cannot be lightly discarded, since following massive hemorrhage it remains a valuable procedure, whether or not vitamin K has been administered.

Although it appears that etiologic and therapeutic considerations in hemorrhagic disease of the newborn are well understood, such is not true with a certain group of cerebral hemorrhages which generally cause death between two and six days after birth. Presumably, injury or anoxia in association with poor clotting power of the blood are concerned in etiology. It is well known that in addition to a low plasma prothrombin level at birth the newborn child suffers further depression of this level between the second and sixth days. The exact part each of these two factors, initial injury and low plasma prothrombin level, plays in etiology is not clear.

Dr. Eastman has now shown that antenatal administration of vitamin K to the mother causes a significant decrease in the number of cerebral hemorrhages both fatal to and contributory to the death of the newborn, and in the number of retinal hemorrhages. His work has been so well controlled that one tends to agree with the suggestion that routine antenatal administration of vitamin K to the mother be given an adequate trial.

Since the plasma prothrombin level is an index of vitamin K activity, it would be interesting to know what were the levels in the babies of this series, especially those who died. With such data, considerable light might be thrown on the relative parts played by trauma, anoxia, and low plasma prothrombin in the production of cerebral bleeding. From a practical standpoint we should know if it is desirable to secure adult or nearly adult levels of plasma prothrombin in the newborn. On the other hand, may it not be sufficient merely to prevent the depression of the level which occurs between the second and sixth days?

Until extensive data on plasma prothrombin levels, correlated with clinical observations, are available so that those babies who need additional vitamin K can be readily recognized, it seems reasonable to administer it directly to all babies or indirectly to the mother before the onset of labor. In view of the greater fetal gain from treatment of the mother compared with direct administration to the newborn infant, as shown by Eastman and his associates, perhaps it is better to employ the former method, at least for the time being. Apparently no observer has yet reported harm to either mother or baby from therapeutic doses of vitamin K administered to either. Certainly, the cost of the drug is not a barrier to its routine use.

Certain problems concerned with bleeding in the newborn may well be elucidated by future work. For example, in view of the comparatively rich content of vitamin K possessed by leafy vegetables and grasses, and their general availability during the summer and early fall, one should look for a seasonal fluctuation in the number of cerebral and retinal hemorrhages in the newborn.

Although routine administration of vitamin K will prevent hypoprothrombinemia in the newborn and thus inhibit a certain amount of slow bleeding, it cannot prevent the basic injury which originated the bleeding. Granting that in many instances this basic injury may be insignificant, nevertheless follow-up studies to ascertain the ultimate outcome of these babies will surely be desirable.

sence of other pathologic changes; the clinical course of the case was at variance with the view that they were secondary to anoxia, although such a contention cannot be disproved. In regard to the three cases (Nos. 6, 9, and 10) in which pulmonary hemorrhage was encountered at autopsy, such findings have been subject to various interpretations; certain observers attribute them to a hemorrhagic diathesis which kills the infant before other organs are involved; others regard them as evidence of an overwhelming pneumonia, while some ascribe them to anoxia. Summarizing Table IV, in 4 of the 16 deaths, hemorrhage appeared to be the direct cause of death; it was present in 5 additional cases and doubtless played a certain role in the fatal outcome, but one which is difficult to evaluate with assurance. In view of the fact that autopsy revealed the presence of hemorrhage in 9 of the control cases and in but one of the vitamin K series, the findings are in keeping with the view that the antenatal administration of this vitamin eliminated a certain number of hemorrhages.

In order to investigate further the efficacy of antenatal administration of vitamin K in diminishing hemorrhage in the newborn, a series of observations was made on the retinas of infants in these two series. These studies were carried out by Dr. Alfred E. Maumenee, of the Department of Ophthalmology, who will presently report them in detail.

A preliminary survey shows the following figures: Among 92 infants in the control group, retinal hemorrhage was demonstrable in 29 cases, or in 32 per cent; among 75 infants in the vitamin K series, there were 12 retinal hemorrhages, an incidence of 16 per cent. The frequency of retinal hemorrhage in the control group, accordingly, was twice that in infants whose mothers had been treated prophylactically with vitamin K. Statistical analysis shows that these figures are significant, the chances being 82.5 to 1 against the likelihood that the difference in the two series is due to sampling error.

What, now, are we to conclude from these observations? Most fundamental is the fact that present-day plasma prothrombin studies have given us a new conception of hemorrhagic diathesis in the newborn. Far from being a disease entity unto itself, it represents simply an extreme degree of a condition, hypoprothrombinemia, which all newborn infants exhibit to a certain extent and in various gradations. Unless the plasma prothrombin level is extremely low, this hypoprothrombinemia may be without clinical manifestations. However, if birth trauma, anoxia, and other causes of bleeding are superimposed upon it, this prothrombin lack must necessarily play a part in the duration, and, therefore, in the extent of the bleeding. Along with trauma and anoxia, then, hypoprothrombinemia must be regarded as a factor in the outcome of every case of bleeding in the newborn, whether cerebral or otherwise; and it is the one factor in this triad, let us recall, which is subject to prophylactic correction. To what extent will the routine antenatal administration of vitamin K diminish hemorrhage in the newborn and thereby reduce neonatal mortality? We believe, in the first place, that such a practice, properly timed and with suitable dosage, will well-nigh eliminate so-called hemorrhagic disease of the newborn. In the second place, the facts indicate that certain types of cerebral hemorrhage, particularly small hemorrhages which ooze over a number of days, may be preventable by this procedure. To what slight extent the elimination of such deaths would diminish neonatal mortality, it is obviously impossible to state, but the evidence presented would seem of sufficient promise to warrant recommending the routine antenatal administration of vitamin K for trial.

In the Charity Hospital in New Orleans we have 350 or more deliveries a month, all in the very low level economic group. We happen, however, to be in a region where because of our climate practically all patients can obtain proper diet at any time of the year. Would it be, in Dr. Eastman's opinion, worth while to give these patients prophylactic vitamin K in spite of that? The economic phase of the question comes up there because of the additional expense.

DR. BECK.—In answer to Dr. Caldwell's question but on the basis of incomplete studies I might say that thus far we have noticed that there is some diminution in the hemorrhages with the use of oxalic acid, although it is not as great as with vitamin K.

DR. FRED L. ADAIR, Chicago, Ill.—I would like to ask whether some of these effects are not due really to a deficiency diet in the patient, and whether it may not be unnecessary to extend this treatment to all people in all economic strata.

In both series were all babies alive when the vitamin K was administered to the mothers?

DR. LOUIS M. HELLMAN, Baltimore, Md. (by invitation).—Dr. Eastman asked me if I would answer some of the questions.

In response to Dr. Mengert, I am sorry to say that, inasmuch as the method used for the analysis of prothrombin requires 3 to 4 c.c. of blood, we have not been able to obtain levels on all the infants that died. Those that we did determine were all low.

As to the question of seasonal variation, Dr. Waddell of the University of Virginia has noted a seasonal variation in the prothrombin of both mothers and infants. We have found the same to be true. This obviously should be so, especially in Baltimore, where a large percentage of the negro population lives on a marginal diet consisting largely of vegetables in the summer and canned goods in the winter.

Dr. Beck's slide showed a hemorrhagic tendency in some of the infants born of treated mothers. This has been our experience too, and is well demonstrated by the studies on retinal hemorrhage. In our clinic this type of hemorrhage occurs in about 32 per cent of newborn infants. The hemorrhage is of the oozing variety and not due to capillary rupture. It should therefore be prevented by raising the prothrombin level; and in the series of infants of treated mothers, the incidence of retinal hemorrhage was reduced to 15 per cent. These infants did not have elevated prothrombins, in spite of the fact that the mothers had received vitamin K. On the other hand, in a small series of 15 deliveries where the mothers had received 2 to 4 mg. of vitamin K daily for four or five days prior to delivery, there were no retinal hemorrhages and the prothrombin levels of the infants were very high in each instance. And thus, in response to Dr. King's question, while the results are good when therapy is given during labor, it would seem that the optimum time of administration should be the last week of gestation.

For the determination of prothrombin, we have used the method of Smith, Warner and Brinkhous, described in 1934. Roughly this method consists of the removal of all substances in the plasma related to clotting except the prothrombin. An artificial clot is then made by adding standardized reagents to various dilutions of this prothrombin. The dilution necessary to form a clot in fifteen seconds determines the dilution unit. While this procedure is very accurate, it requires a skilled technician. The quick method is much simpler and yields essentially similar results. It is certainly much more applicable to clinical work.

Dr. Kosmak asked about the administration of barbiturates in the two series reported. About one-third of our ward patients receive some sort of analgesia. The incidence was the same in both groups.

When vitamin K is administered directly to the newborn infant, we have used 1,000 units or $\frac{1}{2}$ mg. a day for four days. This can be divided between the feedings. However, the prothrombin level of infants can be elevated to a greater degree by administering the vitamin to the mothers prior to delivery. This may be merely a matter of absorption, and perhaps some of the parenteral substances,

DR. ALFRED C. BECK, Brooklyn, N. Y.—Several years ago observations in our Clinic seemed to indicate that the incidence of intracranial hemorrhage and hemorrhagic disease in the newborn were increasing. Because a large percentage of our patients were on relief and accordingly might well have had deficient diets, the possibility of a dietary deficiency as the cause of this increased hemorrhagic tendency was considered. Soon after the early work on vitamin K appeared, we therefore undertook a study somewhat similar to that which Dr. Eastman has reported. Every third service patient, accordingly, was given 2 mg. of the synthetic vitamin K by mouth one hour or longer before the birth of her child. Another third of our patients received oxalic acid, as suggested by Dr. Schumann before this Society. The remaining third was used as controls, the three series being carried on concurrently.

Vitamin K was given to 504 women, and 612 concurrent patients were observed as controls. In the vitamin K series, 4 newborn infants had intracranial hemorrhage and 2 additional ones had bloody stools, making a total of 6, or 1.2 per cent, which might have had a hemorrhagic tendency. In the control series, 11 newborn infants had intracranial hemorrhage and bloody stools were observed in an additional 9. In contrast with the K series, therefore, 20, or 3.2 per cent, of the control babies had hemorrhagic tendency. In other words, bleeding occurred almost three times as often in the babies whose mothers did not receive vitamin K as a prophylaxis.

This slide* is a graphic representation of the effect of the prophylactic administration of vitamin K on the prothrombin activity of a newborn infant. The figures on the base line represent the prothrombin activity as a percentage of that which is observed in the normal adult. The perpendicular figures indicate the number of cases. Your attention is called, first, to the three control graphs in the lower half of the slide. These represent the results of 300 prothrombin determinations made in 100 cases on the first, second and fourth days after birth. In order that you may understand the graph more clearly, this block represents eight cases whose prothrombin activity was from 30 to 40 per cent of the normal. This block represents 31 cases whose prothrombin activity was 70 to 80 per cent of the normal. The perpendicular line is the mean of the entire polygon. As you may observe, the mean of the hundred controls on the first day was 72.6 per cent. This mean fell to 59 per cent on the second day and returned to 72.3 per cent on the fourth.

The upper half of the slide shows the results of analogous observations made on another hundred infants born to mothers who had had the prophylactic administration of vitamin K. In this group, the mean prothrombin activity was 92.9 per cent of the normal on the first day, 90 per cent on the second, and 91 per cent on the fourth. In other words, the prophylactic use of vitamin K seemed to prevent the diminished prothrombin activity which normally is observed on the second day of life. By preventing this fall in the prothrombin level, the tendency to hemorrhagic disease must be diminished, as was shown by Dr. Eastman in his clinical observations and as has been corroborated by our observations in a somewhat larger number of cases. In addition, this slide shows a very pronounced shift to the right in the vitamin K cases. On the first day, as well as on the critical second day after delivery, the number of infants with a low prothrombin activity was much smaller in the vitamin K series than in the controls.

DR. GEORGE W. KOSMAK, New York, N. Y.—I would like Dr. Eastman to tell us whether any patient of this series received barbiturate analgesics?

DR. WILLIAM E. CALDWELL, New York, N. Y.—I would like to know about Dr. Beck's results with the use of oxalic acid in order to follow up the discussion of last year.

DR. E. L. KING, New Orleans, La.—I would like to ask about three points: (1) The determination of the prothrombin level; (2) the time to begin the administration of vitamin K to the mother before delivery; and (3) the advisability of giving vitamin K to infants, delivered by mothers who have not had vitamin K, before circumcision, especially if the coagulation time is slow.

*This slide will appear in a paper to be published in a later issue of the JOURNAL.

THE MANAGEMENT OF THE ADHERENT PLACENTA IN THE PRESENCE OF INFECTION*

KARL M. WILSON, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry)

THE abnormally adherent placenta may at times constitute a very serious problem. Opinions still differ in regard to the length of time one should wait for separation to occur before resorting to manual removal of the organ, provided there is no associated active bleeding; but, in general, nearly all authorities now feel that at least one to two hours should elapse before a manual removal is resorted to unless active bleeding should necessitate its earlier performance. The reason for delay before resorting to manual removal is, of course, to be found in the dangers attending this procedure and in particular the possible resulting infection. The mortality attending this procedure has in the past been placed at around 10 per cent, which would obviously place the procedure in the definitely hazardous class of obstetric operations. To avoid these associated dangers, some have even suggested that in the absence of bleeding, much longer periods of time than the usually accepted one or two hours should elapse before resorting to manual removal. In 1915 the late John O. Polak rather startled the members of this Society by presenting a case in which the placenta was allowed to remain in situ for four days before it was finally removed by expression, and in the absence of bleeding, he recommended waiting indefinitely, days if necessary, before resorting to manual removal.

On the other hand, a number of Scandinavian and French authors have recently presented fairly large series of manual removals with a much lower mortality than has hitherto been recorded. Thus Schie, in Oslo, found in 189 such procedures the mortality included only three patients, or 1.58 per cent. In each of these three instances, death was due to puerperal infection, and it is interesting to note that in two of these women, the manual removal was apparently performed in the presence of an already existing infection.

Personally, I still regard the procedure as a dangerous one, though I accept the usual indications of hemorrhage or delay in separation beyond two hours with no bleeding as sufficient reason for carrying out manual removal. As already pointed out, the particular menace attending manual removal of the placenta is to be found in infection. Undue prolongation of the third stage of labor to many hours or even days, may as in Polak's experience, be at times quite innocuous, but on the other hand, it may also result in the very situation that we are trying to avoid, namely the invasion of the uterus by pathogenic organisms.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

available now only for experimental purposes, should find a field in infant administration. The question seems to be the advisability of attempting to control cerebral hemorrhage which may have already done considerable damage. We have had two rather unfortunate instances where babies with cerebral hemorrhage have received vitamin K. In both cases the babies lived, but they will never develop normally. I think that it is far better to treat the babies yet unborn, through the mother and thus protect them during labor.

Replying to Dr. Adair's question as to whether the babies in these two series were all alive on admission, the answer is that we eliminated all cases where the fetal heart could not be heard on admission to the delivery floor.

Also in reply to Dr. Adair, it has been very well shown by many workers that all newborn infants have a low prothrombin. It would certainly be practical to treat all mothers in labor, even if it were only to prevent hemorrhagic disease. As a matter of fact, the only deaths on our service from hemorrhagic disease, since the use of vitamin K, with the exception of the case mentioned by Dr. Eastman, have occurred on the private service where vitamin K is not routinely used.

DR. EASTMAN (closing).—I should like to make it clear that the major part of this work on vitamin K was done by Dr. Louis M. Hellman and Dr. Landrum B. Shettles, of our Department of Obstetrics, whose names will appear as co-authors of the paper.

of a premature living child, weighing 1,880 Gm. The amniotic fluid escaping after the birth was greenish in color, and had an offensive odor. Cultures taken at the time later showed a mixed growth of organisms with *Strep. viridans* and non-hemolytic streptococci predominating. The blood cultures were negative. After delivery of the child there was no bleeding and the placenta failed to separate. After one-half hour the Credé maneuver was resorted to without success, and several succeeding attempts also failed. She was given a sedative and allowed to rest, but was kept under constant supervision. Under ordinary circumstances manual removal would have been resorted to, but in the presence of the obvious infection this seemed contraindicated. Twenty-four hours later there was no change in the uterus and no bleeding. The temperature fell to normal, but later in the day another chill occurred with a temperature elevation to 40° C., and the patient appeared quite ill. Other attempts at Credé's expression were unsuccessful. Forty-eight hours after delivery she expelled a small clot, the first bleeding that had occurred, but again efforts at expression failed. The temperature continued elevated but was tending to decline. On December 30, ninety hours after delivery, she expelled the intact placenta spontaneously along with approximately 200 c.c. of blood. Her further convalescence was uneventful, the temperature subsiding immediately and remaining at a normal level for the remainder of her hospital stay. During her febrile period before separation of the placenta, two small transfusions were given.

Microscopic study of the placenta revealed extensive inflammatory reaction in the subamniotic connective tissue, and a section stained for bacteria showed numerous short gram-positive chains and diplococci in this same region. Little inflammatory reaction was discovered in the body of the placenta and none at all in the decidua. The decidual layer was quite thin, but there was no evidence of undue penetration of it by proliferating chorionic villi.

In this patient, the source of the infection is undoubtedly to be found in the premature rupture of the membranes with the long interval elapsing between that occurrence and the onset of labor with the resulting invasion of the sac of the ovum by pathogenic organisms. Such intrapartum infection is also a menace to the child from the possible so-called "placental bacteriemia," as emphasized by Slemons. It is of interest to note in this connection that a culture of the cord blood showed the presence of colon bacilli. The baby, however, did extremely well and was discharged from the hospital after five weeks, weighing 2,950 Gm.

COMMENT

In these two patients the end result was quite satisfactory following a conservative line of treatment, and the result would appear to justify the treatment followed. The problem of the adherent placenta and associated infection may well be compared to the infected incomplete abortion. In this latter condition we have had many serious experiences in the past as the result of interference during the period of active infection, and unfortunately many years elapsed before the profession came to an appreciation of the risks involved and abandoned interference except in the presence of active bleeding. At present if there be no associated hemorrhage, we never think of removing the retained placental tissue in the incomplete abortion until several days after the evidence of infection has subsided, and the results following such conservative therapy are far superior to those obtained during the period when active intervention was the rule. It would seem reasonable to apply similar rules to the situation under consideration, that is, wait until the infection has subsided and then resort to manual removal. At the same time we must admit that the menace in the case of the adherent full-term placenta with associated infection is greater than would be the case in the earlier abortion. The risk is greater because, if a.

When infection is already established in the presence of an adherent placenta, the problem becomes still more formidable. In reviewing the literature on the subject, I was surprised to learn how little attention has been paid to this angle of the problem. In current textbooks, Adair alone makes mention of the added menace, but Eastman also draws attention to it in his recent review of the literature on obstetric hemorrhage.

I propose to present two examples of this complication which occurred on my service with an outline of the procedures followed.

CASE 1.—L. M. (Unit No. 115282), aged 23 years, para iii, all previous labors normal. In this, her fourth pregnancy, she was delivered spontaneously in her home by her physician, two days before admission to the hospital. Numerous efforts at the Credé maneuver were unsuccessful, and there was no associated bleeding. After forty-eight hours, she was given gas oxygen anesthesia, and an attempt was made to remove the placenta manually. This was unsuccessful but did cause considerable bleeding so she was then sent to the hospital May 22, 1936. On admission she appeared to be gravely ill; temperature, 39.3° C.; pulse, 170; blood pressure, 85/50. She presented a waxy white appearance and was obviously suffering from the effects of hemorrhage and infection, though bleeding at the time of admission was slight. Red blood count was 2,690,000; hemoglobin, 6.2 Gm.; white blood count, 18,100. In view of the history, some consideration was given to the possibility of placenta accreta, but she was obviously in no condition for a major operation, so efforts were directed toward improving her general condition by transfusion and the other usual general measures. Six hours after admission and fifty-four hours after delivery, she spontaneously expelled the bulk of the placenta, but there was an obvious defect in it, representing an absence of tissue from an area of about 8 by 4 cm. The expulsion of tissue was accompanied by the loss of approximately 150 c.c. of blood and no further bleeding occurred. Her general condition had improved somewhat at this time, but was still precarious, so it seemed unwise to adopt any immediate measures for the recovery of the retained fragment of placenta. Twelve hours later this remaining fragment was expelled spontaneously with no associated bleeding. Her convalescence was stormy, with evidence of serious infection persisting for four weeks, and she developed a mild thrombophlebitis of the left leg during the puerperium. Blood cultures were persistently negative. She eventually recovered and was discharged from the hospital six weeks after admission.

Microscopic examination of the placenta showed no unusual invasion of the covering decidua by the chorionic villi. An acute placentitis was present with fairly extensive leucocytic infiltration throughout.

She was seen again last year, when she aborted spontaneously at six months with no attendant complications.

CASE 2.—L. G. (Unit No. 121075), aged 32 years, para i, had had one miscarriage. Her first pregnancy was terminated in another city by induction of labor at term, apparently on account of a toxemia. The child died immediately after birth, and the patient sustained a third degree tear which was later repaired. Her second pregnancy terminated in early spontaneous abortion. In her third pregnancy she was first seen by me on July 19, 1938, when she was about two months pregnant, the calculated date of confinement being Feb. 23, 1939.

This pregnancy proceeded quite uneventfully until Dec. 18, 1938, when the membranes suddenly ruptured. She was promptly admitted to the hospital. On admission she was not in labor, but the membranes were obviously ruptured. The uterus was the size of a seven months' pregnancy, and the fetal heart sounds were normal. She presented evidence of a slight upper respiratory infection, but apart from this her general condition was satisfactory. There were no further developments for seven days, when she began to have irregular painful uterine contractions. Coincident with the onset of labor she had a chill and a temperature elevation to 39.5° C. Labor progressed very slowly, apparently on account of irregular and inefficient uterine contractions, but after thirty hours she was delivered spontaneously

Manual removal of the placenta is the usual method of procedure for such a condition, and generally speaking, this may be resorted to if after two hours, in the absence of bleeding, the simpler methods have failed to bring about separation and expulsion of the organ. Undue prolongation of the third stage may well result in the very accident we are trying to avoid, namely, partial separation with hemorrhage or invasion of the uterus by pathogenic organisms. Should bleeding occur, resort to this procedure may be necessitated earlier.

In the presence of associated infection however, manual removal of the placenta becomes a truly hazardous procedure and should not be employed during the period the infection is active unless active bleeding supervenes and necessitates interference. Occasionally supravaginal hysterectomy may be the preferable procedure. Attention is drawn to the delay in the onset of lactation while the placenta remains attached to the uterine wall.

REFERENCES

Adair: Textbook of Obstetrics and Gynecology, 1940. *Eastman, N.*: Obstetric Hemorrhage, New International Clinics 3: Series 2. *Polak, John O.*: Trans. Am. Gynec. Soc., 1915. *Schie, E.*: Acta obst. et gynec. Scandinav. 19: 28, 1939. *Stemons, J. Morris*: J. A. M. A. 65: Oct. 9, 1915.

DISCUSSION

DR. GEORGE KAMPERMAN, DETROIT, MICH.—We have for a long time accepted the principle that puerperal patients with fever should be treated very conservatively. An exception to this policy has been found only in certain cases where bleeding was of such proportion as to constitute a hazard.

On looking over the records of patients at Harper Hospital who had retained placental tissue with fever and excessive bleeding, we were rather surprised by the almost uniformly good results obtained by the removal of the retained placental tissue. In the last four years we have records of seven such patients treated actively, and all made rapid recoveries without complications or spread of infection.

We have, therefore, gradually developed a wider indication for interference in patients with the known retention of placental tissue. We are inclined to believe that the known retention of placental tissue in a patient with fever speaks for the diagnosis of sapremia rather than sepsis.

With this process of reasoning in mind I would like to report two patients about whom we were consulted during the past year. Both were delivered in their homes by their family doctors, and the failure of expulsion of the placenta called for consultation and later hospitalization. Both patients had had high fever for several days and seemed very septic and very ill. In both the Credé technique of placental expression had been repeatedly unsuccessful. Both patients were very anemic, although bleeding had not been a prominent symptom. One patient showed a positive blood culture, while in the other no blood culture was obtained. In both cases the placenta was removed by digital separation and extraction with a placental forcep. In one case the placenta was removed seventy-five hours after delivery, the temperature being 104.8° F. before delivery. Temperature dropped to almost normal within two days with an occasional rise for six days after that. In the second case the placenta was retained for nine days post partum, the fever rising to over 104° F. for several days before the removal of the placenta. Two days after the removal the temperature was normal and remained normal.

It would seem to us that the emptying of the uterus in such cases would favor involution and contraction and would tend to close the sinuses and lymphatics, and thus lessen the spread of infection.

To avoid these serious and trying situations it would seem there is no time so favorable for the removal of an adherent placenta as when the patient is clean and fresh. Theoretically, there is danger in invading the uterine cavity; yet with

partial separation should occur during the waiting period, the hemorrhage might well be much greater than would be the case in the earlier pregnancy. For this reason, and because it might occur quite suddenly, the patient should never be left unattended while the placenta is still in utero, and preparations to facilitate immediate interference should be kept constantly available.

In this situation, if partial separation with hemorrhage should occur, one's hand is forced. If the emergency is serious, it may be necessary to disregard the menace of infection and remove the placenta manually at once to prevent further hemorrhage, or on occasion it might seem preferable to control the bleeding temporarily by packing the uterus, and then resort to abdominal hysterectomy. Either will be hazardous, and the choice of procedure will depend on the circumstances present at the time the emergency arises.

In considering factors possibly responsible for prolongation of the third stage of labor, three main possibilities must be considered, and it is important to make proper differentiation between them. Thus, the placenta may separate and yet be retained in utero by the contraction ring; it may be abnormally adherent; or more rarely, we may be dealing with a true placenta accreta. Differentiation between the first two of these conditions is usually not difficult. Recognition of a placenta accreta, however, can only be by manual exploration of the uterine cavity, and the diagnosis is usually established on discovering the impossibility of removing the placenta manually. In both of our patients, consideration was given to the possibility of a placenta accreta being present, but in the first patient her condition was too critical at the time of admission to permit exploration of the uterus; while in the second, we felt that the infection present contraindicated exploration. In our second case then, the diagnosis was held in abeyance until the problem solved itself by spontaneous separation and expulsion of the placenta.

In these two patients, we were quite confident from the evidence at hand that we were dealing with abnormally adherent placentas and not simply with retained placentas; but in the second case, in particular, an additional late observation gave convincing evidence that this was the situation. This later observation was made in connection with the establishment of lactation, which did not occur until the third day after the placenta had been expelled or the seventh day after the birth of the child.

Such an observation appears to support the current theory that the onset of lactation may be due to a deprivation of certain hormonal substances originating in the placenta, possibly estrin or progesterone, or both, and that lactation is held in abeyance while these are being actively produced, which would be the case while the placenta is in active organic union with the maternal organism.

SUMMARY AND CONCLUSIONS

Two examples of abnormally adherent placenta and associated infection are presented. Both were treated conservatively but both made good recoveries.

A COMPARISON OF TWO CESAREAN SECTION SURVEYS CARRIED ON IN THE CITY OF NEW ORLEANS*

EDWARD L. KING, M.D., NEW ORLEANS, LA.

IN 1927 the New Orleans Gynecological and Obstetrical Society¹ reported the findings of a survey of the 300 cesarean sections performed in the city during the six years 1921 to 1926, inclusive, discussing the indications, techniques, results, etc. In 1938² the Society presented a review of the 1,108 sections performed in New Orleans during the ten years from 1927 to 1936, inclusive. We felt that this second survey would be of interest as a method of ascertaining whether the lessons learned from the first study had been taken to heart by the local profession. A review of these two investigations is presented to this Society, as I believe that the improvement in results demonstrates the value of a frank presentation of such data. I also feel that the Society would be interested in a consideration of the changes in thought and practice in this matter of cesarean section as shown by these two sets of figures.

TABLE I. 1921-1926

Total deliveries in city	61,966
Total deliveries in hospitals	16,323
Total cesarean sections	300
Cesarean percentage of total deliveries	0.48
Cesarean percentage of hospital deliveries	1.8
Cesarean, total deliveries ratio	1 to 206

Table I shows that in the first period of six years there were 16,323 hospital deliveries with 300 cesarean sections, an incidence of 1.8 per cent. The total deliveries in the city during this period were 61,966; cesarean section accounted for 0.485 per cent of these. In other words, in these six years one out of every 206 babies was delivered by the abdominal route. In Table II, covering the succeeding

TABLE II. 1927-1936

Total deliveries in city	92,936
Total deliveries in hospitals	52,629
Total cesarean sections	1,108
Cesarean percentage of total deliveries	1.19
Cesarean percentage of hospital deliveries	2.08
Cesarean section, total delivery ratio	1 to 84

ten years, we see that there were 52,629 hospital deliveries, with 1,108 sections, or 2.08 per cent of the total. There were 92,936 births in the city during this period; of these, 1.19 per cent were delivered by cesarean section. Thus, in this second group, one out of every 84 babies reached the world by laparotomy. In the first survey, it was found that approximately one-fourth of the total deliveries were in hospitals; in the second study, this ratio had increased to a little over one-half; and in the last three years of this time, two-thirds of the obstetric patients

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, Seigniory Club, Que., June 17 to 19, 1940.

proper technique and asepsis this is a fairly safe procedure. During the past three years we note 19 cases of manual removal of the placenta in the delivery rooms at Harper Hospital, and a careful study of the records shows no shock and no fever resulting in these 19 cases.

We believe a frank puerperal sepsis and puerperal fever due to an adherent or retained placenta are two different conditions. From the experience we have had with active interference where we thought it was indicated because of bleeding, we believe that the known retention of placenta, as well as the bleeding, should be considered an indication for active treatment.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—On the Obstetric Service of the Bryn Mawr Hospital during the past three years, there were 6 patients with retained placentas for more than twelve hours after delivery. All were primigravidas from 21 to 39 years of age. Four of the patients had sodium amytal or rectal ether analgesia, and two patients had no anesthesia at all. Two were delivered by low forceps, two delivered spontaneously, and in two rotation of a posterior occiput was practiced.

Our attitude toward a retained placenta after delivery has been the same as toward secundines which are not expelled after a miscarriage. The patients are placed in semi-Fowler position, given sedatives, ergot, and blood transfusions if these are indicated. Intrauterine packing is resorted to if the bleeding is profuse.

All of these patients had some fever. In three cases the temperature was over 104° F. and was accompanied by chills. In several instances where attempts at manual removal of the placenta were made, such efforts were invariably followed by an exacerbation of symptoms. All of our patients recovered, passing the placenta spontaneously; one on the second day, two on the fourth day, one on the fifth day, and two on the sixteenth day. We are convinced that patients with retained placenta should be treated conservatively.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—I would like to disagree with the idea that the placenta in utero has any restraining influence on lactation. Dr. Peter Freuchen who wrote that very interesting book, *The Frozen North*, reports many cases of Lapland women who, while nursing one baby, will become pregnant with another, nurse that one and again become pregnant at the same time, repeating this all their lives. If there were any evidence of the placenta influencing lactation it would be shown in these women.

There is a difference between a retained placenta and an adherent placenta, and a placenta increta. We know that the whole placenta may be safely left in the clean uterus, in the absence of hemorrhage, for several days. Ramsbotham even reports a case where the placenta did not come away at all, and he believed it had been absorbed, as it may be in ectopic pregnancy. On the other hand large pieces of the placenta may come away more or less broken up, in the lochia. An adherent placenta may require some time to separate, but usually bleeding demands treatment. Placenta increta is a different matter, for in these cases the placenta has grown into the muscle.

Dr. Wilson has proved that the post-partum uterus will handle more infection than we give it credit for. In septic abortion I have packed the cervix and vagina to stop bleeding, given blood to replace the previous loss, and thus tided the patient along until her immunities have been developed or until it was safe to invade the inflamed uterus. I wonder if such a policy would succeed with a full-term pregnancy. Would sulfanilamide be useful in such cases?

DR. E. L. KING, NEW ORLEANS, LA.—We have at times injected the placenta with about 200 c.c. of normal saline through the umbilical vein, and this has seemed to help in the separation of these retained placentas (Gabaston-Mombojou method).

DR. WILSON (closing).—Since one accepts the principle that one should not invade a uterus known to be infected, I continue to wait for separation in the absence of bleeding. On the other hand, if bleeding occurs, one's hand is obviously forced. If that should occur, one has the choice of two procedures, either to remove the placenta or to perform a hysterectomy.

We did not administer sulfanilamide because we did not know until later what organism had caused the infection.

"Inertia with prolonged labor," a rather unsatisfactory reason for the performance of the operation, dropped from 9 to 1.4 per cent. The miscellaneous group covers such conditions as elderly primiparity, malpresentation, previous myomectomy, contraction ring, etc.

TABLE V. TECHNIQUE

	FIRST SERIES	SECOND SERIES
Classical	175	545
Low segment	31	488
Porro	10	39
Portes	0	2
No details as to technique	84	34
	300	1108

Table V presents a tabulation of the techniques employed. The committee felt that the majority of the 84 operations in the first series which were not described in the records were of the classical type, and that thus the proportion was much greater than the 58.3 per cent shown. In the second series, the classical operation had dropped to 49 per cent, with the possibility that some of the 35 which were not described were in this group. The increase in the popularity of the low segment operation is striking, and this tendency is abundantly justified by the low mortality rate following this procedure. Thus, in the first series, the 31 low segment cases all lived, and in the second series, in 488 low operations the maternal mortality rate was 3.7 per cent.

TABLE VI. NONFATAL COMPLICATIONS

	FIRST SERIES	SECOND SERIES
Febrile morbidity (International Standard)	63.5%	61.3%
Pulmonary	9	14
Genitourinary tract	8	28
Acute dilatation of stomach	17	1
Postoperative convulsions (eclampsia)	5	1
Postoperative vaginal hemorrhage (2 deaths from this in first series)	3	3
Evisceration	1	4
Wound infection	11	15
General infection	8	18

Table VI lists the most important nonfatal complications. It is to be noted that the febrile morbidity is practically the same in both series. We were surprised to find that the figures in the second period showed little difference between the classical (63.8 per cent) and the cervical (62.3 per cent) operations. It was felt that the 17 cases of acute dilatation of the stomach in the first group (only one in the second) were in great part really instances of infection, probably peritoneal. The greater proportion of postoperative convulsions in Series I is simply a concomitant of the larger number of cases of eclampsia in this group. The fairly large number of cases of postoperative vaginal hemorrhage were thought to be due in some instances to uterine relaxation, in others to improper technique in suturing the uterus.

In Table VII, the causes of maternal death are listed. The maternal mortality rate was 16.1 per cent in the first series and 5.9 per cent in the second. A considerable part of this reduction is due to the fact that eclampsia has been almost eliminated as an indication. In each group, the mortality rates from peritonitis and septicemia were much too high, and we were greatly disappointed at finding so many in 1937, after pointing out in 1927 that one-fifth of the deaths were due to these two causes. In the second series, these complications accounted for one-third of the deaths. Seventeen of the 41 patients with eclampsia in Series I died, as did 9 of the 27 in the second series. It is to be noted that 3 of the 33 cases of placenta previa

in the city were hospitalized. The percentage of sections in the hospital patients shows a slight rise, but the increase in the proportion of obstetric patients delivered in hospitals was associated with a rise in the percentage of sections to total births to a figure two and one-half times that in the first survey.

TABLE III. PERCENTAGE OF CESAREAN SECTIONS IN VARIOUS HOSPITALS

	FIRST SERIES	SECOND SERIES
New Orleans Charity Hospital	1.2	1.4
Hospital A	1.5	2.3
Hospital B	2.9	1.1
Hospital C	2.7	4.9
Hospital D	2.8	3.0
Hospital E	0.25	0.6

Table III shows the incidence of section in those hospitals from which complete data were obtainable for both periods. It will be noticed that the figures for the Charity Hospital are essentially the same, while there is an increased ratio in most of the private hospitals. In the case of Hospital B, the committee was informed that there were other sections in the second period, the records of which were not secured for study. Complete data might not have shown the reduction noted in the table. It is interesting to observe, incidentally, that in the first period 11.5 per cent of the total deliveries in the city were in the Charity Hospital, and that in the second this percentage rose to 31, the increase being particularly noticeable in the last three years, when the figure rose to 42 per cent.

TABLE IV. INDICATIONS

	FIRST	SECOND
Contracted pelvis	107	480
"Disproportion"	16	71
Cervical and vaginal lesions, benign	10	38
Carcinoma of cervix	1	3
Eclampsia	41	27
Other toxemias	12	51
Placenta previa	33	114
Premature separation of placenta	6	34
Cardiac lesions	4	22
Fibroids of uterus	2	15
Previous cesarean section (with 4 ruptured scars in first and 2 in second)	28	70
Inertia with prolonged labor	28	16
Prolapsed cord	2	0
Miscellaneous	10	167
	300	1108

Table IV presents a comparison of the indications for the operation in the two series. The records were much more specific in this regard in the second period. It will be seen that contracted pelvis accounted for about one-third of the operations in the first series and almost one-half in the second. The rather indefinite designation "disproportion" was noted in about the same proportion in both. The drop in the figures for eclampsia (from 14 per cent to 2.4 per cent) is most striking. We were surprised to find that there had been no increase in the proportion of sections for placenta previa, the percentages being 11 and 10.3, respectively. The committee was under the impression that there had been quite an extension of this indication, and we find that this is true for the past few years. The figures for previous section seem low, but this is accounted for by the fact that many repeat operations were listed under the original heading of contracted pelvis. There were really 50 "repeat" sections in the first series and 148 in the second. The low figures for uterine fibroids and prolapse of the cord are also worth noting.

half that following the classical. Of course, some of the latter may have been done in the more unfavorable cases, because of the greater speed and ease of performance; this could not always be deduced from the record.

TABLE IX. MATERNAL MORTALITY, ANALYZED ACCORDING TO TYPE OF OPERATION
SECOND SERIES

	TOTAL CASES	DEATHS	PER CENT
Classical	545	39	7.2
Porro	39	4	10.3
Portes	2	1	50.0
Low segment	488	18	3.7
Not described	34	2	6.0
	1108	64	

In Table IX the fetal mortality figures are presented, classified chiefly according to the operative indications. When prematurity was the chief cause, the cases were listed under that heading rather than under the operative indication. In the first series 35 per cent and in the second 27 per cent of the fetal deaths were due to this cause. Of course, most of these were in the toxemic and hemorrhage cases; however, under these conditions it is doubtful whether vaginal delivery might not have been feasible.

TABLE X. FETAL MORTALITY

	FIRST SERIES	SECOND SERIES
Pelvic contraction	2	4
Eclampsia, term babies	4	0
Toxemia	3	1
Placenta previa, term babies	4	3
Premature separation placenta	3	3
Congenital malformations	4	3
Neglected labor	5	1
Ruptured uterus or scar	5	4
Tonic contraction of uterus	1	1
Cerebral hemorrhage	1	1
Uterine fibroids	1	3
Asphyxia	0	2
Pneumonia	0	1
"Stillborn," no details	0	8
Prematurity	19	31
Not stated	3	51
	55	117
Per cent	18.9	10.8

SUMMARY

From these two surveys we see that: (1) The incidence of cesarean section in New Orleans was $2\frac{1}{2}$ times as great in the second period as in the first. Two questions naturally arise: Were too few operations performed in the first period, or were too many performed in the second period? Probably both questions can be answered to some extent in the affirmative. However, if 1.4 per cent is the correct figure for the Charity Hospital (it may be too low) to which many obstetric patients are referred because of complications, it would appear that 1.19 per cent for the total number of deliveries in the city is too high a proportion. The same might be said of the 2.87 per cent incidence of cesarean section in the private hospitals as a group.

TABLE VII. MATERNAL MORTALITY ANALYZED AS TO CAUSE OF DEATH

	FIRST SERIES	SECOND SERIES
Peritonitis	6	10
Septicemia	3	12
Ruptured uterus or scar	3	0
Toxemia	3	2
Eclampsia	16	7
Placenta previa	1	2
Pyelonephritis	0	1
Postoperative intestinal obstruction	0	1
Paralytic ileus	0	2
Postoperative shock	0	2
Spinal anesthetic	0	1
Antimony poisoning	0	1
Premature separation placenta	1	0
Acute dilatation of the stomach	2	1
Pneumonia	1	8
Postoperative vaginal hemorrhage	2	3
Heart lesions	2	4
Embolus	5	2
Moribund	0	1
Tuberculosis	0	1
Renal suppression	0	1
Doubtful	2	2
Total	47	64

in Series I and 7 of the 114 in Series II resulted fatally. One of the fatal cases of eclampsia in Series I and 2 in Series II were listed under peritonitis, as were 2 and 5 cases, respectively, of placenta previa. Pulmonary embolism caused 5 deaths in the first group and only two in the second. Two patients in the second series were moribund; one is listed as such, the other patient died of tuberculosis, and her condition was hopeless at the time of operation. These two patients were sectioned for the sake of the babies, both being saved. The case of antimony poisoning requires special mention. This patient was operated upon because of extensive granulomatous lesions of the vulva which precluded vaginal delivery. She was treated pre- and postoperatively by tartar emetic intravenously, and death was ascribed to hypersusceptibility to this drug.

In connection with the review of the maternal mortality, one significant fact was noted. In the first series, 23 of the 47 deaths occurred in patients whose records showed long labors, many examinations, attempts at vaginal delivery, membranes ruptured for many hours, etc. In the second group, these gross errors of judgment were noted in the records in only 11 of the 64 fatal cases. However, as 22 of these 64 deaths were due to peritonitis and septicemia, it is highly probable that the 11 additional patients had also been subjected to contamination from below. It would seem that more attention was paid to the matter of potential infection in the second series, but that none the less the bounds of safety were too often transgressed.

TABLE VIII. MATERNAL MORTALITY, ANALYZED ACCORDING TO TYPE OF OPERATION
FIRST SERIES

	TOTAL CASES	DEATHS	PER CENT
Classical	269	47	17.5
Porro			
Not described			
Low segment	31	0	0

In Table VIII the maternal mortality is analyzed according to type of operation. As noted above, the low segment operation, in the first series, was not followed by a single death, and in the second group the mortality after this operation was one-

More of these comparative studies should be made in order to keep the question of cesarean section, with its still relatively high mortality and morbidity, constantly before the general practitioner, and the general surgeon, as well as the obstetric specialist.

(The tables referred to will be found in the previously published paper by Matthews, Harvey B., and Acken, Henry S., entitled "A Critical Survey of 1,066 Cesarean Sections," in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 38: 956, 1938.)

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—While repetition of a survey after some years affords interesting comparative material, yet it is my feeling that a cesarean section study should be continuous. We have tried to accomplish this in the City of Philadelphia by having hospital obstetric staff conferences meet at regular intervals in each hospital to discuss the current obstetric work.

In regard to their mortalities, the hospital conference is always asked to furnish its own opinion as to preventability and responsibility. Such a frank discussion in a local group tends to tighten up obstetric practice. Furthermore, continuous audit of cesarean deaths carried out before a large group of obstetricians in a city brings out the indications to which exception might be taken, the possible lack of prenatal study, errors in judgment, and technique on the part of the operator.

Although the incidence of cesarean section has increased to a certain extent in Philadelphia, we feel that the marked reduction in mortality in cesarean sections proves the benefit of the continuous review of obstetric surgery.

TABLE I. CESAREAN SECTIONS IN PHILADELPHIA

	1931	1932	1933	1934	1935	1936	1937	1938	1939
A. Total live births	33,773	32,093	29,228	29,751	29,988	29,652	30,059	30,739	30,232
B. Number of cesarean sections	601	591	583	638	703	799	811	795	857
C. Cesarean section rate	1.8	1.8	1.7	2.1	2.3	2.7	2.7	2.6	2.8
D. Cesarean section deaths:									
1. Classical	15	19	14	16	25	15	14	5	6
2. Cervical	4	6	3	4	6	4	5	1	4
3. Porro	1	0	0	0	0	3	1	1	0
4. Unlisted	18	11	6	1	1	6	0	6	1
Total	38	36	23	21	32	28	20	13	11
E. Cesarean death rate	6.1	6.0	3.9	3.1	4.6	3.6	2.5	1.6	1.3

DR. GEORGE KAMPERMAN, DETROIT, MICH.—I am greatly interested in this report because of a similar study made by the late Dr. Walter Welz in Detroit during 1925. His figures were appalling, for he found a maternal mortality of 13 per cent and a fetal mortality of 11 per cent. Since then Dr. Ward Seeley has made a comparative study of cesarean sections in Detroit during 1930 and noted a marked improvement. Five years after the report of Dr. Welz the maternal mortality had dropped from 13 per cent to 4.43 per cent (corrected 3.44 per cent). There had been no improvement in the fetal mortality, however, which was 12.8 per cent in the second report.

In analyzing the statistics it was interesting to see where the improvement had come. The low cesarean section which had in the meantime become much more popular seemed to have been partly responsible for a lower maternal mortality. But in my own mind I am not convinced that that was a great factor. We have become more conscious of the danger of cesarean section in the presence of infection, and that consciousness developed just about the time when we began to substitute the low cervical section for the classical section. It would seem that knowing when not to operate was an important factor in the improvement. More important still seemed to be the fact that eclampsia was no longer considered an indication for cesarean section, and I think this change was the chief cause for the improvement in maternal mortality.

2. The indications are more clearly set forth in the records of the past few years, and on the whole seem to be more judiciously placed in the second series.

3. The overstepping of the bounds of prudence in the second series was much less pronounced than in the first, but there is still much room for improvement.

4. The superiority of the low cervical operation is clearly shown.

5. The Porro operation should probably have been performed more frequently, as it is to be noted that 22 of the deaths in the second series were due to infection.

6. The newly developed technique for the performance of true extra-peritoneal section should aid in further reducing the mortality.

7. The reduction in mortality rates (maternal and fetal) is gratifying, but both figures are still too high. We believe that there has been a further improvement since the presentation of this second report, but have not yet received the figures of the past three years.

8. It is felt that such surveys are of distinct value, especially when repeated every few years, and that such "stock-taking" benefits the profession in general and the obstetric specialists in particular.

REFERENCES

- (1) New Orleans M. & S. J. 79: 815, 1927. (2) Ibid. 90: 731, 1938.

DISCUSSION

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—As Dr. King very clearly pointed out, the second study in the City of New Orleans showed a very great improvement over the first survey, and we feel sure that this would be true of other communities. In going over histories prior to ten years ago we found very different histories as compared with those being taken today. Better histories bring improvement in diagnosis and more strict indications for cesarean section. Along with these improvements there must necessarily be improvement in operative technique as well as in the choice of operation.

By way of comparison, I desire to refer to a series done at the Methodist Hospital by one group of men, 18 in number, all trained along somewhat the same lines. The total deliveries were 27,234 in eighteen years. The total mortality was 3.18 per cent, which of course is very much lower than Dr. King's series, but to be expected from a selected group of men. This is neither the lowest nor the highest mortality rate for cesarean section done under the conditions under which this series was performed.

The fetal mortality in our series was 5.2 per cent. In Dr. King's first series, it was 18.9 per cent and in the second 10 per cent. The latter shows a vast improvement but is still not as low as it would be in a group of more highly trained obstetricians. Furthermore, it brings out the point that cesarean section does not necessarily guarantee a live baby, a fact not generally recognized.

Another study showed the general improvement attained by a specialized group working over eighteen years and shown in 3 six-year periods. The mortality rate steadily declined. Dr. King's study brought out this fact although not as strikingly. Furthermore, the superiority of the low-flap operation is strikingly brought out in our series as it was in Dr. King's.

Our indications for cesarean section run about the same as in Dr. King's series. This would tend to show that indications are fairly well standardized and if rigidly adhered to would undoubtedly reduce the present-day morbidity and mortality rates. Naturally, the competency of the operator and adequacy of the operating facilities will always be of prime importance.

is the better. I have to read long galleys for the Year Book every year, in which is presented to me a digest of the literature on obstetrics all over the world. The impression I get is that the old classical operation should be pronounced obsolete. From the Year Book pages, there is a continual succession of statistics showing the greater safety, even in the hands of the modern general surgeon, of the low cervical operation, which gives better results for clean as well as infected cases.

The mortality statistics of Dr. King agree with those I get from the literature and those of Dr. Holmes fit very nicely into the picture also. I believe that the rates of the abdominal delivery are so high that the medical profession will have to do something about it. If we doctors do not do something to improve the conditions under which women have babies, either the public or the Government will, and it is time for us to clean our own house first.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—The point I wish to discuss is the difference between the results obtained in the low cervical and the classical cesarean section. There is only one way to decide the matter and that is for one operator to do both operations in alternate cases. In our clinic I have just completed 200 cesarean sections, and every other one has been done by the classical alternating with the low cervical. The operations were performed in the same room. I opened and closed the skin personally. The same nurses and interns were in attendance, and the patients received the same preoperative and postoperative care. The result of the study is that, so far as I can determine, there is practically no difference between the two operations.

In analyzing the amount of postoperative distress, one-twelfth of a grain more of morphine was used to keep the patients who had classical cesarean sections comfortable than was used for those who had low cervicals.

We had two deaths, one of which was not due to the operation. As in Dr. Davis' case, the wound was perfectly healed but the patient died of a chronic nephritis, which was the reason for the operation. The other was an infected case in which the patient died of the infection. We feel that the evidence from this series for the low cervical is not very strong and in the hands of the same operator about the same results will be obtained.

DR. FRED L. ADAIR, CHICAGO, ILL.—In the first place, I do not believe that cesarean section in itself is a particularly dangerous operation if the operator is competent and the cases are properly selected. Any maternal mortality in excess of 1 per cent and any fetal mortality in excess of 2 per cent is too high. While the indications for cesarean section have changed, the contraindications have not changed materially. The excessive mortality in most hospitals is due not so much to an extension of the indications as to the neglect of enforcing the contraindications for this operation. In any institution, the obstetric staff together with the hospital authorities should see to it very definitely that the contraindications are very closely observed with regard to cesarean section. That is the safest way to keep the mortality within proper limits.

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—I very recently made a survey of 343 cesarean sections in my own group, consisting of seven men, all of whom were teaching in Northwestern University. In this series of cases in which the contraindications had been very closely observed, we had a mortality of 0.88 of 1 per cent. Hence, under favorable conditions I think the operation can be carried out with a high degree of safety.

DR. KING (closing).—There is a much larger percentage of cesarean sections performed in hospital practice than in private practice. For instance, we had 1.14 per cent of cesarean sections in all deliveries in New Orleans, and 2.8 per cent of the hospital deliveries were by cesarean section. The series of others give us about the same figures.

Improvements must also be considered as partly due to dilution of the figures. Thus in the first series 1 out of every 204 babies was born by cesarean section, whereas in the second series this proportion was increased to 1 out of every 86.

DR. CARL HENRY DAVIS, WILMINGTON, DEL.—During the last year I have gone over the records of my private obstetric practice in Milwaukee, checking the results in various types of cases. I found a cesarean incidence of 4.8 per cent in the private group. At the Milwaukee County Hospital where we had our teaching cases, the incidence was 1.9 per cent. My fetal mortality in cesarean deliveries compares very closely with that of Dr. Matthews.

Curiously, I found in checking the temperature morbidity that in my classical cesarean sections there was a slightly lower percentage of morbidity (51 per cent) than in the low cervical cases (60 per cent), and that with the Porros, which were largely done in women who had had previous cesarean sections and wished to be sterilized, I had the most favorable morbidity rate of all, fever occurring only once in six cases.

I believe the reason for the improved results in my classical cases was that I have followed the same technique that we use in the low cervical operations, namely, to avoid the use of packs and to employ suction for removing fluid and blood. There was one death, due to an unrecognized postoperative appendicitis with ileus, in 73 cesarean sections. Cultures of the interior of the uterus were entirely sterile, so that I do not believe the patient died as a result of the cesarean section but as a result of the appendicitis.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—It is a self-evident fact that cesarean section has a minimal mortality rate only when there have been no antecedent medical complications or obstetric difficulties. Contracted pelves or true disproportion alone of all obstetric indications gives cases with this minimal operative risk. With all other indications there is a dual hazard, the operative risk and the danger inherent in the indicating complication.

Of course, the unindicated or "expedient" operations on healthy women will be followed by a negligible mortality rate. Therefore, the man who holds himself to strict indications for cesarean section will always have a definitely high mortality rate. It is just as irrational for the obstetrician to mass all his cesarean sections irrespective of the indications as it would be for the abdominal surgeon to so group all his laparotomies.

Figures on cesarean section garnered from 335 hospitals in 1929 showed that 292 women died following 4,889 sections, a rate of 5.97 per cent. I showed the table to the actuary of one of our largest insurance companies. His first query was, "How many hospitals had no cesarean deaths? As you are dealing with the problem of cesarean mortality, it is improper to include the hospitals which lost no mothers." The table was therefore revised. In 161 hospitals, there were 1,625 operations without a maternal death. Therefore, in 174 institutions there were 3,264 operations with 292 deaths, or 8.95 per cent. Of these, 29 hospitals had 1,269 operations with the loss of 42 mothers, 3.3 per cent. The remaining hospitals, 145, had 1,995 sections with a mortality of 12.5 per cent, which constituted 31.3 per cent of all puerperal deaths. Again, in 97 (55.7 per cent) of the 174 hospitals with a mortality, 161 deaths occurred, or 20.7 per cent. In 18 hospitals with 43 operations 35 mothers died, or 81.4 per cent.

I presented to certain authorities the interesting fact that as the numbers of annual births decreased in hospitals the cesarean mortalities rapidly increased until in 7 with 8 operations no mothers survived. Most men agreed that the men in those hospitals neither knew when or how to perform the operation. One gave a different explanation. "In those small hospitals the operations were performed on necessitous indications. In our clinic we carefully select the cases and the majority of the operations are dictated by expediency."

I imagine that most of the decline of mortality in New Orleans was due to the elimination of eclampsia as an indication. How much of this decline also is the result of a prohibition of sections being performed by general practitioners? In northern hospitals where such a ban is in vogue, the incidence of cesarean has fallen and the mortality rate has declined.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—I am particularly interested in the discussion of the relative virtues of the low cesarean section as compared with the old classical operation, and I am in a peculiarly favorable position to determine which

PSEUDOHERMAPHRODISM*

J. P. PRATT, M.D., DETROIT, MICH.

(From the Department of Obstetrics and Gynecology of the Henry Ford Hospital)

HUMAN interest is attracted by the unusual. Formerly hermaphrodites were curiosities who found it difficult to establish a satisfactory and useful place in society. These unfortunates being neither male nor female were buffeted from one classification to the other, often becoming social outcasts in spite of their keen mentality. Development of genetics, embryology, biology, and endocrinology has benefited these misfits, and study of the hermaphrodites has added to our knowledge of these sciences.

Hermaphrodite is an ambiguous term which originated with the ancient Greeks. A child born to Aphrodite and Hermes possessed the sexual attributes of both father and mother. Appearing to be a combination of both, it was called "Hermaphroditos." Hence, hermaphrodisism signifies a combination of male and female in the same individual.

True hermaphrodisism exists when the same individual bears both male and female gonads and is capable of impregnating a female and of being impregnated by a male. This state is characteristic of many lower form of animals, e.g., the earthworm. Its occurrence in man is exceedingly rare.

Young¹ cites Photakis as asserting positively that such classical hermaphrodisism has never occurred in man in contrast to Neugebauer's citation of ancient literature where the tragedy and comedy of true hermaphrodisism were recorded. Omitting the proof of ability to impregnate or be impregnated as essential to true hermaphrodisism, Young¹ collected reports of 20 cases proved microscopically. Five had an ovary on one side and an ovotestis on the other; 4, a testis on one side and an ovotestis on the other; 3, an ovotestis on one side and the character of the gonad on the other side undetermined; 6, an ovotestis on each side; and 3, a testis in the scrotum on one side and an ovary in the pelvis on the other.

Pseudohermaphrodisism exists when gonads of only one sex are present, but the appearance of the rest of the genital organs does not clearly indicate the true sex. Several classifications have been prepared to express the numerous combinations found. Since no two cases reported are alike, detailed terminology becomes complex. It is simpler to classify according to the nature of the gonad.

During the past three years, I have been one of a group to observe three male pseudohermaphrodites. The only characteristic belonging to all three cases was the presence of male gonads.

CASE 1.—E. W., aged 17 years, first seen June 30, 1937, complained that she was a hermaphrodite and wanted to know what could be done to make her more like a girl. In general, the patient had been healthy and had never experienced any

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

Thus it is apparent that many more favorable cases were included in this second series. That naturally helps us to bring down the mortality rate.

It appears that the low section is the preferable operation as shown by our figures as well as by others, and, of course, the results are better, because the low sections were practically all done by specialists. Dr. Falls states that he obtained as good results from classical as from low sections. All of his cases, however, were either elective or the patients were operated upon early in labor, and under such circumstances equally good results, after the two types of operation, are to be expected. In the patients who have been in labor for some time I feel that it is well established that the low operation will give the best results. Again we must not overlook the subsequent obstetric history of these patients, for I feel that it is well established that rupture of the scar is more frequent after the classical operation.

There is no question that the selection of the cases is of vital importance. The mortality rate of the obstetrician is low, not because the specialist is a better operator than the general surgeon, but because he avoids the infected cases and selects those patients suitable for cesarean section. Note that one-third of the deaths of the second series was due to septicemia and peritonitis. This proportion would have been much lower if the proper selection of patients and operation had been more carefully practiced. The situation as regards eclampsia was much improved in the second series. In the first series there were 41 cases of eclampsia with 16 deaths, which amounted to one-fourth of the total fatalities, whereas in the second series there were 27 cases and 7 deaths.

The Committee has recommended that all hospitals in New Orleans adopt the procedure of requiring a consultation for all cesarean sections. However, some of the private hospitals have not come to that point of view.

the clitoris became erect, it always curved downwards, the curve being exaggerated by erection. About one-half teaspoonful of material was obtained by masturbation. Nocturnal emission occurred about once in two weeks. She considered the structures in the scrotum to be testes because she had obtained semen from the vagina (urethra) (Figs. 1 and 2).

Examination, when she was first seen on June 30, 1937, showed a tall, lanky individual of light complexion. Her extremities, hands and feet, were long; height was 5 feet, 9½ inches; weight was 135 pounds. The light brown hair was slightly curly. Hair distribution was mixed, masculine and feminine with feminine distribution of pubic hair. Development of fine hair on the limbs was conspicuous. Development of the hair on the face suggested a masculine tendency. Considerable acne marred the face and back. The light gray eyes showed normal reactions and

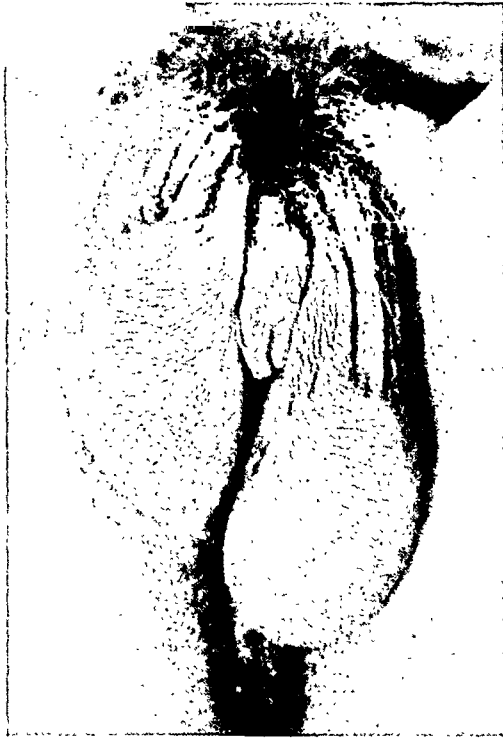


Fig. 3.—Case 1. Preoperative. Shows saddle scrotum and rudimentary penis.

movements. Nose was relatively large and pointed. Teeth were normal. No general glandular enlargement was noted. The thyroid cartilage was prominent. Heart and lungs were normal. Pulse was 80 and blood pressure 120/78. Reflexes were active. A midline laparotomy scar appeared below the umbilicus.

Skeletal Development.—The bones of the extremities were long and heavy. The spine was straight. The hips were broad and the pelvis was feminine.

X-ray Examination.—The sella turcica was normal in size and shape. The bones of the skull were normal. The pelvis was rather large, but the sacrum was somewhat lower between the ilia than is ordinarily the case in a woman's pelvis. The epiphyses at the knees were closed, and the epiphyses of the radius were only recently closed though still visible.

Rapid development of the scrotum and contents noted at the age of 9 had continued to increase. The saddle scrotum contained a gonad on each side. The wrinkled skin over the scrotum was deeply pigmented. The erectile organ 4 cm. long, curving downward, resembled a penis with a dimple at the tip representing the meatus. The urethra opening at the base of the penis was thought by the patient to be a miniature vagina. The voice was high contralto. The breasts, de-

serious illness. She was born in East Prussia. At birth the doctor told the family that she was a female child though not quite normal. When the child was four months old, the family moved to Essen. When she was a year old, her parents consulted a gynecologist in Königsberg. He said that she was an abnormal female but should wait until the age of puberty before anything was done. When she was 4 or 5 years old, they saw other doctors in Germany who likewise advised waiting until puberty. When she was 5 years old, her family migrated to America. They consulted several physicians in this country who likewise advised postponing any



Fig. 1.

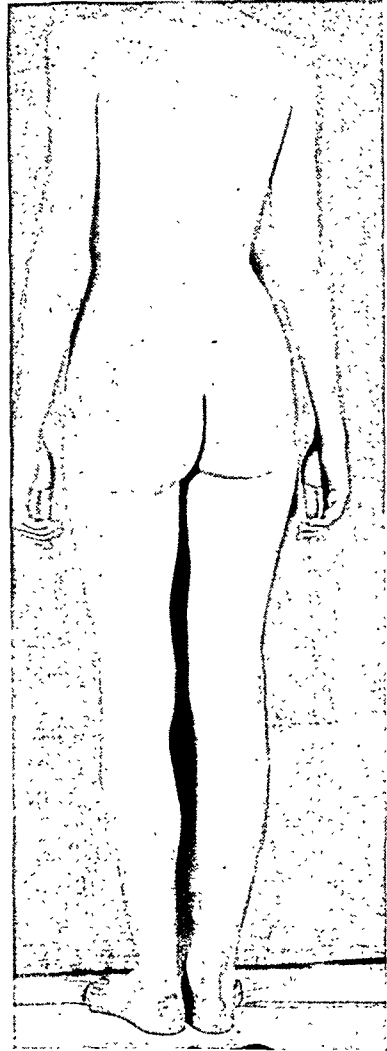


Fig. 2.

Fig. 1.—Case 1. Front view, preoperative. Shows feminine pubic hair, scrotum, previous laparotomy scar, female breasts, and masculine extremities.

Fig. 2.—Case 1. Rear view, preoperative. Shows female pelvis, narrow waistline, and masculine extremities.

operative procedure until puberty. During childhood her family considered that she was distinctly feminine in appearance and in behavior. At the age of 12 she consulted another physician who likewise advised waiting. When she was 14 years old, a laparotomy was performed. Rudimentary organs were found "all messed up together." No uterus was present. The operator thought that there might have been a rudimentary vagina. The appendix was removed at that operation. She was given some sort of pituitary preparation by injections with no apparent effect. Erections of the clitoris began at the age of 10. She had noticed that when

bladder. The tunica over the gonad was incised for inspection of the gonad. There seemed to be a well-defined epididymis between the testis and the vas. Careful inspection of the gonad showed a smooth surface. Two hydatids were seen on the upper pole (Fig. 5). No structures resembling a corpus luteum were seen. A few areas were suggestive of Graafian follicles. If the gonad were an ovotestis, the distribution of the tissues must have been intimately mixed. On inspection there was no portion of the gonad which appeared distinctly different from the rest of the structure. A very small piece of the cortex was excised for microscopic study. In order to prove the structure of the gonad, it would be necessary to remove one entirely or to take a section the full length of the gonad. This did not seem justified. The gonad together with the vas was dropped into the retroperitoneal space and the incision closed in the usual manner for repair of a hernia. On the left side the same procedure was carried out except that the whole tunica was removed and carried with the gonad to the retroperitoneal space. There was ample room for the gonads in the retroperitoneal space. They were well protected in this position. This operation was done for the purpose of permanently elevating the temperature of the gonads in order to diminish their testicular function and to permit the scrotum to collapse, thus appearing more like labia. Postoperative course was uneventful.



Fig. 5.—Case 1. At operation. Shows structure like a testis, hydatids, vas and spermatic vessels ready to transplant into hernia incision.

Following the operation the pigmentation over the scrotum diminished. The tissues shrank so that it became possible to do a plastic to reconstruct the tissues to resemble labia instead of scrotum. Following the operation the breasts enlarged. The clitoris or penis remained the same size. The possibility of erection and of masturbation was still retained, though almost no fluid was obtained by masturbation. The voice seemed a little lighter in quality and her family were convinced that it was more feminine. The hair on the face continued to be a source of great annoyance. Electrolysis was tried but without great satisfaction. Patient has since resorted to a depilatory.

Plastic operation for construction of labia and covering of clitoris or penis was done on Aug. 8, 1938: An incision was made in the midline between the saddle scrotum; the raw areas were brought together across the midline to increase the amount of tissue resembling a mons veneris. The redundant foreskin was adjusted to cover the penis or clitoris. This was nearly hidden by the tissue. The urethra still opens underneath the erectile organ. At the same time the broad scar from the patient's former laparotomy was excised to make a more sightly scar (Fig. 6).

The patient became satisfied with her state after the two operations and felt that she could go among other girls in the locker rooms and gymnasium without hesitation. Her behavior became more and more feminine. A normal interest in

veloped more than would be expected for a male and less than for a female, showed definite ducts opening on the nipples. A rudimentary prostate was felt on rectal examination (Figs. 3 and 4).

Examination by Dr. Cothran, July, 1937: "The penis appears to be about normal size for a boy of 7. The foreskin is well back off the glans and could be considered as labia minora. The opening of the urethra is in a position which would be comparable to the peno-scrotal junction in a normal male. The scrotum is almost completely divided in the midline. Gonads are about normal size for the age of 17. The vas can be palpated.

"*Cystoscopic Examination.*—The bladder capacity is normal. The bladder wall is normal with the exception of an area around the neck over the lower trigone where there is a moderate amount of acute but low grade inflammatory reaction. The urethral orifices are in normal position. The urine shows a few pus cells (cultures were negative). There is no elevation at the base of the bladder which

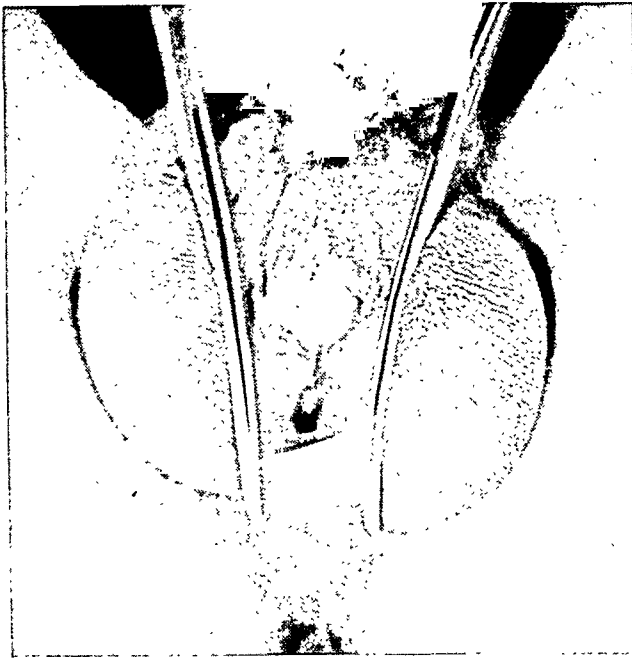


Fig. 4.—Case 1. Preoperative. Shows urethral opening at penoscrotal junction; dimple representing meatus on rudimentary penis.

would suggest the cervix pushing in. The bladder sphincter seems to work well. In the posterior urethra is a structure which is apparently a verumontanum. The small prostate is massaged and a small amount of clear fluid obtained. This contains 10 pus cells per low-powered field."

Laboratory studies showed normal urine; blood Wassermann, negative; hemoglobin, 90 per cent; red blood cells, 4,850,000; sodium, 342; chlorides, 453; cholesterol, 196; albumin, 4.37; and globulin, 1.52. Glucose tolerance test revealed a delayed utilization of sugar and a phosphorous curve obtained when insulin is lacking. Three basal metabolic rates were within normal limits. The temperature at all three readings was subnormal (97°, 97°, 96.4° F.). The respiratory quotients were 0.82, 0.79 but dropped to 0.77 one-half hour after the administration of glucose. Hormone studies showed no estrogens or androgens in a single specimen before operation. The dilution was too great to give a positive test.

Operation.—Aug. 10, 1937. Transplantation of gonads from scrotum into the abdomen. An incision was made over the right inguinal canal, opening the extraperitoneal space. On opening the cremaster a cord containing vessels and vas was exposed. This cord extended upward from the gonad, passing through the inguinal canal into the retroperitoneal space toward the midline at the base of the

one motivating drive: 'Lately, I had a sex dream in which I was playing the female part; it made me decide I was going to do something about it, and that's why I came to the doctor.' The patient's mood changes were of adolescent type, with a rather strong tendency to the reflective and introspective side. Her estimate of herself was at low ebb. Her adaptability to social demands and to her environment generally was very good. The dynamic nature of her personality organization may be judged from the fact that she was the president of her class, the business manager of the school paper, the manager of the school secondhand store, and member of several honor societies. Her conduct and deportment were, at all times, acceptable. Her responses to standard tests are informative. Dr. Schott reported the following: On the Thurstone Personality Schedule, she made a total point score of 65, indicating some degree of emotional maladjustment. On the Northwestern Introversion-Extroversion Scale, she made a total point score of 618, which is slightly above the midline toward the extroverted end of the scale and very significantly on the Terman Masculinity-Femininity Test, she made a total point score of 'plus 28, which, when compared to the norm for high school juniors (patient has just finished junior year in high school) is more masculine than 95 per cent of girls, and as masculine as approximately 20 per cent of the boys of junior standing in high school.'

"On Aug. 10, 1937, the patient had her first gynecologic operation. Psychologically, there immediately set in a favorable metamorphosis of her personality. Endocrinologic factors probably added their part shortly after. For the next year, we watched the gradual disappearance of the patient's guilty feeling of deception, and saw her keenly looking forward to her plastic operation by Dr. Pratt on Aug. 9, 1938. Shortly after, she openly declared herself a female who could pass general inspection. These self-found assurances soon registered the disappearance of excessive self-consciousness to a point where re-examination was postponed until the recent months, February to May, 1940. That she has become progressively more feminine is clearly evident in patient's spontaneity and initiative toward all manner of things of feminine interest. Questioning, both direct and indirect, brings answers that need no discounting. Although it might be said that much of patient's personality is conceivably due to purposeful striving and constant training, yet we cannot escape the fact that the motivation for such striving arises within the same individual who was previously so gropingly masculine. Standardized psychology determinations are now reported by Dr. Schott as follows: Re-evaluation of the patient's intellect during February again gave her a very superior rating, with an I. Q. of 146 (chronologically, 20 years, 3 months). On the Northwestern Introversion-Extroversion Test, she made a total point score of 605, 'which is very close to the midline of the scale, or just 5 points toward the extrovert end. This is very close to her previous score of 618.' On Terman's Masculinity-Femininity Scale, now very significantly, in comparison to the norms given by Terman for sophomore girls in college, gives patient a rating of -116, which is in the fifth percentile for college sophomore girls; and being thus to the minus side means that the patient now rates as feminine as 95 per cent of the women in her group. This is essentially a full reversal of her previous showing on this same test.

"The patient aspires to additional educational attainments, and understandingly hopes that marriage may not be denied to her."

CASE 2.*—E. K., aged 15 years, first seen Feb. 13, 1937, complained of a left inguinal hernia which had been present since birth. In earlier years of life there was an umbilical hernia which disappeared spontaneously. Six days before admission the patient complained of a sharp attack of pain in the left inguinal region associated with some vomiting. He was away at school. The school physician who examined him stated that the hernia was partially strangulated, but it was reducible by manipulation. A truss was advised until vacation. For several years the patient had noticed a mass descending into the left scrotum on straining, but it had always been reducible.

*This case is presented through the courtesy of Dr. W. W. Noel, formerly of the Surgical Staff of the Henry Ford Hospital, now of Henderson, N. C.

boys developed. Before the operation she hesitated to test herself for fear that if she gave way to her inclination to go out with boys she might be disappointed and all would be lost. She was greatly relieved when she found that she had a normal reaction to the company of young men.

*Hormone Assays.**—"Urine samples 3-18-40, representing two days' collection of urine, and 4-1-40, representing 4 days' urine, were assayed for androgenic activity by the castrate rat method and for estrogenic hormone by the Allen-Doisy method.

"Both samples gave a negative estrogenic reaction when tested at 40 I.U. and 25 I.U. per day levels, respectively; that is, they contain less than 40 I.U. and 25 I.U. per day equivalent or less than 80 I.U. per sample.

"Sample 3-18-40 gave a weakly positive androgenic response at 25 I.U. and negative at 50 I.U. per day equivalent.



Fig. 6.—Case 1. Postoperative. Shows enlarged breasts, and scrotum converted to resemble labia.

"Sample 4-1-40 gave a negative response at 25 I.U. per day equivalent or 100 I.U. in the whole sample."

Personality.†—"During our first observations and examinations of this patient between June 30 and Aug. 10, 1937, we were always impressed by a particular type of demeanor. Here was an individual in woman's attire. When addressed, she immediately reflected a guilty apprehensiveness which carried in it the implication, 'I'm masquerading; I'm not what you think I am.' To us, her deception was less clear than her reflection of culpability. After several office visits, this implication of moral turpitude gave way to a representation of intellectual alertness. She was keenly interested in the details of her intelligence tests, as carried out by Dr. Schott, and she was rightly pleased when he evaluated her at the Superior Adult Level, with an I. Q. of 139, with her chronologic age at 17 years and 7 months. Her instinctive urges and affective cravings seemed poorly formulated except for

*Assays of urine by Dr. D. A. McGinty.

†Personality observation by T. J. Heldt, psychiatrist, and E. L. Schott, psychologist, Henry Ford Hospital.

Operation.—Radical repair of the left indirect inguinal hernia was done by Dr. Noel on Feb. 18, 1937. The structures of the inguinal canal showed nothing unusual. At the time of operation the hernia sac was empty. The left testis was brought into the incision by traction. The testis was not accompanied by an epididymis. The vas deferens was small and poorly defined. The vas was lying between layers of peritoneum close to a structure that proved to be a uterus. When the uterus was brought into the incision, it resembled a normal uterus in contour, the size being below normal for the age of 15. Tubes were present, and the gonads were in the usual relative position of ovary to tubes. A cordlike vas, which seemed to fray out in the broad ligament, was present on the right side but did not communicate directly with the gonad (Fig. 8). The gonads were dissected from the uterus and tubes. The right gonad was dropped back into the peritoneal cavity, the raw areas having been covered with peritoneum. The left gonad was brought down into the left side of the scrotum. A section was taken from the gonads for microscopic examination. The uterus, tubes, and a portion of the vagina were excised. The vagina extended downward, penetrating the peritoneum. Apparently, it ended at the urogenital fascia. A greater portion of the vagina was excised with the uterus. The postoperative course was uneventful.

From the time of the operation in February, 1937, to November, 1937, his height had increased to 6 feet and his weight to 180 pounds. His masculine appearance increased. There had been an increase in the growth of body hair.

Pathologic Diagnosis.—Male reproductive system: infantile testis and epididymis; rudimentary uterus, Fallopian tubes and cervix, hermaphroditism.



Fig. 8.—Case 2. Taken at operation. Shows uterus, tubes, and gonads exposed through a hernia incision.

Tissue consisted of uterus, tubes, vas deferens, and gonad found in a fifteen-year-old male.

The specimen consisted of an irregular mass of soft fibrous tissue covered mostly by a thin endothelial tissue. This resembled somewhat an underdeveloped uterus. On either side rudimentary Fallopian tubes projected. These tubes had no demonstrable lumina. The "uterus" was a muscular tube with a soft mucosal surface 1 to 3 mm. in thickness. Another flat plaque of tissue with a soft mucosal surface was also present.

Microscopic: Section through the testis and epididymis showed small tubules with no active spermatogenesis. Very little mitosis was noted within the lining of the seminiferous tubules. The interstitial cells were quite large in the sections examined. The epididymis was essentially normal.

Sections through the vas deferens also appeared normal.

Section through the structure which was grossly identified as uterus showed the character of an infantile uterus in which there was a tall, columnar, epithelial lining with several irregular glandular structures in the mucosa. The stroma of the mucosa was rather fibrous. Muscle fibers were abundant throughout.

The Fallopian tubes showed a number of villous processes and also were surrounded by muscle fibers.

Positive findings in the past history were measles and influenza without complications; mastoidectomy at the age of 7; indefinite history of urticaria, hay fever, and asthma. There was a history of frequent colds and sore throats.

General physical examination showed a well-developed boy of 15; height 5 feet 10½ inches; weight 160 pounds. He showed a normal masculine development. The body contour was distinctly male. The penis was normally developed. Distribution of hair was masculine. No enlargement of the breasts was noted. No general signs of femininity were observed (Fig. 7). Left maxillary sinus was slightly cloudy. Examination of the heart and lungs was normal. Blood pressure was 105/65. No masses or tenderness in the abdomen was demonstrated. Skeletal development was normal. The features of the face were rather fine. There was no suggestion of a beard. He had done well in school. Examination on admission showed a complete left inguinal hernia, but the right scrotum was empty. Palpation of the right inguinal

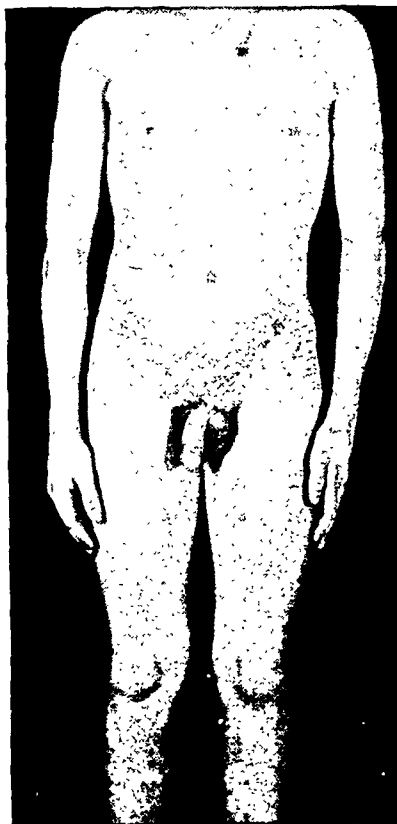


Fig. 7.—Case 2. Postoperative. Shows normal male torso, extremities, and genital organs. The discoloration of lower abdomen and groin is due to antiseptics and dressings for operation.

canal suggested the presence of an undescended testis. Otherwise the examination was essentially negative. It was noted that the voice was somewhat high-pitched; some slight suggestion of feminine behavior, though nothing definite, was stated.

Rectal Examination.—Prostate was small, but no seminal vesicles could be palpated. The pubic hair showed a feminine distribution. The boy had noted frequent erections during the past two or three years. There were nocturnal emissions as often as once every two weeks. He admitted masturbation but not excessive. He preferred the company of males, but appeared to have a normal male reaction to females.

Laboratory Findings.—The blood Wassermann was negative; hemoglobin, 88 per cent; and urinalysis, normal. No hormone analyses of urine were made in this case.

assume that in the absence of a uterus the hormones are utilized in a different manner than in normal individuals; that the hormones have been present in larger quantities in the past but at present are minimal; that the balance of the hormones causes their destruction in the body so that they are not recovered in the urine.

An attempt to estimate the hyper- or hypofunctions of the other glands may be questionable, but if one can be permitted to interpret the findings of blood chemistry, it might be assumed that there were mild degrees of hypothyroidism, hypoinsulinism, and mild grades of overactivity of the pituitary and adrenal cortex. Many of the physical characteristics are consistent with the overactivity of the pituitary or adrenal cortex. The blood pressure-raising principle of the adrenal medulla has not been in excess. There was some apparent interference with normal utilization of glucose which might be due to pituitary antagonism or insulin lack. The interpretations of the function of these are largely speculative.

A prolonged discussion of the biologic, embryologic, and genetic relations is not possible here. These special fields are ably presented by Young¹ in his monograph and by the authors of several chapters in *Sex and Internal Secretions*.²

The social status of pseudohermaphrodites is a matter of prime importance. The study of our three cases by a group resulted in no unanimity of opinion as to what should be done with them. In Case 1 the majority felt that the individual should be transformed as much as possible to the female type; the opposite view was held by the minority. In Cases 2 and 3 the operators felt that the patients' best interests were preserved by not telling them or the family of the true conditions. The majority group opinion was against this and probably will prevail. It would seem that the judgment of the psychiatrist should be given a great deal of weight in any consideration of the treatment of pseudohermaphrodites. Following is a comment by Dr. Heldt:

"These pitiful individuals are more nondescript in their own feelings than they are on physical inspection. Although they have the right to the best that science has to offer, they are often shunned, socially ostracized, and avoided, if not maligned, by layman, surgeon, and physician alike. The foregoing cases clearly illustrate the fallacy of such an attitude. It is probably not so much surgical courage that is needed as it is sociologic understanding. The surgeon hesitates to undertake plastic operations on these individuals lest he be open to malpractice suits. Such suits are too often born of the greed of some poorly qualified attorney and the abject ignorance of the public. These cases are not as rare as you may think. Every psychiatrist can point to several during the course of his years of practice. Here are two: An individual in his forties with ample penile organ, but small scrotal contents for years masqueraded as a woman cook in city hotels. His sparse barba permitted him to let his hair grow long in imitation of a woman. All his feelings, attitudes, and desires were feminine. During recent years, because of his fear of "being found out," he has been compelled to dress as a man. He is very miserable. In the privacy of his own room he lives the life of a woman. Repeatedly, he has beseeched physicians and surgeons for a plastic operation to convert him into a woman. He has always been denied. Another individual, late in his thirties, has a liberal penile organ, apparently rudimentary testes, but withal, large and pendulous breasts. Because of same, he is forced to dress as a woman and to live

Portions of the plaque of tissue (vagina) removed from the pelvis showed a covering of a single layer of tall columnar epithelium with considerable amount of mucin. Mucous glands were noted in the stroma which in addition contained muscular fibers and fibrous tissue.

CASE 3.*—G. K., aged 20 months, was seen on July 29, 1937, as an emergency on account of a strangulated, left inguinal hernia. The child had been previously observed at the age of 17 months for acute suppurative mastoiditis, tonsillitis, and pharyngitis. A mastoidectomy was done May 6, 1937, which healed completely in about one month. Tonsillectomy and adenoidectomy were done June 4, 1937, from which the patient promptly recovered.

At the time she came to the hospital for the mastoiditis, she was wearing a truss for bilateral inguinal hernia which was said to have been congenital. The parents were advised to have the hernia repaired. The patient was taken to the country to recuperate following the mastoidectomy and tonsillectomy. She was readmitted as an emergency on June 29, 1937, because the left hernia had become strangulated. The symptoms present were swelling, pain, and vomiting. The parents had been warned of the possibility of strangulation; therefore, they came promptly for attention.

Physical Examination.—The patient was a light blond with curly, flaxen hair. The examination was summarized by "a normal female infant." Weight was 24 pounds.

Operation by Dr. Lam, July 29, 1937: The left inguinal canal was opened. The mass in the canal had been partly reduced by relaxation under anesthesia. Cloudy fluid was noted in the hernia sac on account of the strangulation. Since the child had a normal external appearance of a female, the operator was much surprised to find a vas deferens, rudimentary testis, and epididymis. The structures were removed. The intestine recovered its tone and no operative procedure was necessary for it. The hernia was repaired.

Operation on August 3, 1937: Repair of right inguinal hernia. The structures in the inguinal canal were incised. On opening the cremaster a rudimentary testis, epididymis and vas were found, quite similar to the ones which had been previously removed from the left side. They were placed extraperitoneally under the transversalis fascia. The hernia was then closed. The pelvis was explored and no evidence of uterus, tubes, or ovaries was found.

Microscopic sections were reported by our pathologist to be those of infantile testis, epididymis, and vas deferens of normal structure, showing no pathologic change. Postoperative course was satisfactory. Patient has not been observed since then.

DISCUSSION

The three cases reported are classified as male pseudohermaphrodites, because in each instance the gonads were testes. In Case 1 there may be a possibility of true hermaphrodism on account of a suggestion of Graafian follicles seen by gross inspection, but this observation was not supported by microscopic examination. The excretion of sperm established the existence of testes.

Endocrine studies of pseudohermaphrodites would be enlightening, but, unfortunately, only a few have been reported. Hearty cooperation of the patient in Case 1 permitted complete investigation, while Cases 2 and 3 were discovered at operation and special studies were limited because neither the patients nor their families were aware of the true condition.

The minimal findings of sex hormones in Case 1 are not consistent with the development of the individual. Theoretic speculation might

*This case is presented through the courtesy of Dr. C. R. Lam of the Surgical Staff of the Henry Ford Hospital.

A case which I reported some years ago is very similar to that presented by Dr. Pratt this morning, except that the cryptorchidism in my case already existed, while in Dr. Pratt's case it was surgically produced. My own patient exhibited typical female psychology and libido, although her only gonads were testes. There was no vagina, and later I constructed a satisfactory artificial canal. In my own case the heterosexual gonads were removed, although, were I to encounter a similar case now, they would probably be left. We are getting away from the idea that the male sex hormone is diametrically antagonistic to the female, as we now know that one and the same gonad can produce both male and female sex hormones.

Finally, as Dr. Pratt has well stressed, the sociologic factor must be the guiding one in the management of these cases and much less attention should be given to the sex of the gonad than to such considerations as the patient's psychology, and the sex in which she has been brought up. It would be a cruel and unjustifiable procedure to try to convert into the opposite sex an individual who has lived as a female for many years, merely because she happened to have a male type of gonad.

DR. PRATT (closing).—The first patient had no vagina, and the urethra opened directly at the junction of the penis and perineum. There was not even a cloaca. By endoscopic examination the vas could be seen emptying into the urethra. After operation a little fluid could still be obtained by masturbation, but spermatozoa were no longer present in the fluid

the life of one. However, all of his feelings are those of the male. Due to his pseudo-rôle as a woman, his fears have ostracized him to the point that he avoids the medical profession.

"The case of E. W. here reported by Dr. Pratt discloses the value of surgical and medical assistance. Psychiatrically, it is judged that more than 60 per cent of E. W.'s transformation is due to the patient's alteration in mental attitude and personality organization upon a background of objective alteration granted her through surgery. It is judged that only a small 40 per cent can be credited to any estrogenic hormones that might be present. Rich though this field be in satisfaction for the plastic surgeon, it is greater still in its humane implications."

REFERENCES

- (1) *Young, H. H.*: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, 1937, Williams & Wilkins Company. (2) *Allen, E.*: Sex and Internal Secretions, Baltimore, 1939, Williams & Wilkins Company.

DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—There are two classes of pathetic individuals who have benefited by the newer knowledge showing the bisexual qualities of the individual, namely the pseudohermaphrodite and the sexually perverted. There is no doubt that both classes have been somewhat mistreated in the past. Often the pseudohermaphrodite has been subjected to early damaging surgery simply to confirm a diagnosis, the activating motive more than likely being curiosity rather than surgical judgment. Irreparable harm may be done by such unwise procedures.

That Dr. Pratt resorted to psychiatric consultation is not surprising and the value of this move is evident. Painstaking effort was made to find out what the individual desired and what sexual path offered more hope. In the past, the opposite was often true. The operator and family usually made the decision for the individual and the resulting agreement sealed the decision.

We regret, with Dr. Pratt, that complete hormone assays could not have been done. However, in view of other studies on individuals of this age it appears quite doubtful if these would have been conclusive. Until we know more about the source, utilization and metabolism of the androgens in the female, one could not interpret such results critically. For the same reason it would seem wise to withhold the androgenic products as therapeutic agents in the female.

We have treated surgically two pseudohermaphrodites at Duke Hospital in the past five years. One was quite similar to Dr. Pratt's first patient and in this case our results have been entirely satisfactory. The other patient was a "man" who was small and psychically derelict when we first saw him. The social agencies, the police court, and the family were anxious to have "him" converted into a "male." Plastic operations on the clitoris and scrotum created fair external genital organs, but also created intense resentment. The subsequent course has been one of continuous lawlessness, meanness, and intractability. The individual undoubtedly really wanted to be and should have been helped to become a female.

Dr. Pratt's thorough case studies point to the fact that these individuals should have sympathetic and prolonged handling before surgical procedures are elected. His paper offers two distinct contributions, the utilization of the body heat in the abdomen to diminish the male gonad function and the consultation with the psychiatrist early in the treatment.

DR. E. L. KING, NEW ORLEANS, LA.—Did this girl have anything like a vagina and was any attempt made to obtain fluid after operation to ascertain if it contained spermatozoa?

DR. EMIL NOVAK, BALTIMORE, MD.—The external sex characteristics in these cases of pseudohermaphroditism are likely to be of little value in indicating the nature of the gonads. With pretty much the same external sex characteristics, one may find either a male or female gonad.

munication reviews in detail the experimental, human, vaginal inoculations, summarizes the results of attempts to infect various animals, and presents the physiologic data now available. This last phase of the work will be continued.

HUMAN PATHOGENICITY

One nonpregnant and 28 pregnant women were subjected to experimental inoculations of the vagina with varying amounts of the pure culture of trichomonads. From 200,000 to 2,000,000 organisms were introduced, but a variable amount of the inoculum escaped promptly from the vagina. In a few instances, the culture employed for inoculation was relatively old in that active multiplication had ceased. The inoculation, which was carried out through a sterile speculum with the patient in the lithotomy position, was preceded by determination of the pH of the vaginal discharge, using the glass electrode technique,⁵ by smears and hanging drop preparations, and by cultures for gonococci, monilia, and trichomonads. The smears were stained by the Hucker modification of the Gram technique, and the vaginal flora was classified according to Schroeder (Grade I, Döderlein bacilli only; Grade II, Döderlein bacilli plus other bacteria; and Grade III, no Döderlein bacilli). Cultures were made as follows: Gonococci, on chocolate agar according to Carpenter's⁶ technique; "monilia" on Sabouraud's agar; and trichomonads, on placenta agar slants covered with Locke's solution plus 5 per cent human serum.⁷

None of the women used for the experiment presented trichomonads before the inoculation; gonococci were also uniformly absent, but in four instances "monilia" were recovered. The vaginal discharge was classified as Group I in 21, Group II in 7, and Group III in 1 case. The pH ranged from 3.9 to 5.4, and averaged 4.4.

The inoculated women were re-examined periodically for clinical evidence of vaginitis, and repeated culture and hanging drop examinations were made. When successful implantation of the protozoa became apparent, the discharge was studied bacteriologically for the presence of hemolytic streptococci, staphylococci, and colon bacilli.

Twenty of the pregnant women were refractory to attempted implantation of the trichomonads and did not develop any vaginal irritation. This fact argues

TABLE I. TWENTY WOMEN IN LATE PREGNANCY IN WHOM TRICHOMONADS COULD NOT BE IMPLANTED EXPERIMENTALLY*

CASE	AGE	VAGINAL pH	SMEARS	FOLLOW-UP EXAMINATIONS	
				NUMBER	DAY
1	29	4.12	I	2	6-9
2	25	4.59	I	3	4-6-8
3	26	4.13	II	3	4-6-8
4	23		II	4	2-4-6-18
5	21	4.13	II	1	12
6	25	4.32	I	2	3-14
7	23		I	5	2-4-5-6-9
8	22	4.58	I	4	3-5-7-19
9	25	4.39	I	3	3-5-7
10	28	4.30	I	3	3-5-7
11	18	4.41	I	4	2-5-7-9
12	28	4.52	I	4	2-5-7-9
13	24	4.83	II	3	3-5-7
14	27		I	6	2-4-6-9-23-25
15	26	4.42	I	5	3-5-10-12-24
16	27	4.29	I	2	2-7
17	35	3.99	I	2	4-7
18	36	4.23	II	2	2-19
19	23	5.41	III	2	3-5
20	40	3.98	I	2	5-7

*All examinations were negative for trichomonads and no cases of vaginitis developed.

THE PATHOGENICITY AND PHYSIOLOGY OF A PURE CULTURE OF TRICHOMONAS VAGINALIS*

RAY E. TRUSSELL, A.B., AND E. D. PLASS, M.D., IOWA CITY, IOWA
(From the Department of Obstetrics and Gynecology, State University of Iowa)

FOR eighty years after Donne¹ first described the human vaginal trichomonad in 1836, little attention was given to its possible pathogenicity. Hoehne,² in 1916, apparently developed the concept that the protozoon is a pathogen and introduced the term "trichomonaskolpitis" to express this relationship. During the succeeding years, opinion has been strongly divided as to whether the organism actually is responsible for the irritation with which it is associated or whether it is merely living symbiotically with bacteria that produce the inflammation. Previous investigators have shown that "trichomonas vaginitis" can be induced in an uninfected woman by inoculation with the vaginal discharge from one who is infected or with a mixed culture of the trichomonads and associated bacteria on artificial media. Other investigators (Hibbert and Falls)³ have produced vaginal irritation and discharge by inoculations with the so-called *Streptococcus subacidus*, which they claim is frequently present in the "trichomonas vaginitis" discharge, and therefore took the position that the trichomonas is not pathogenic. It has, however, been well recognized that the controversy could not be settled until a pure culture of the protozoa was available for experimental inoculations.

Over the past four years, several workers in our laboratory have conducted innumerable experiments designed to develop a bacteria-free culture of the trichomonads but without success. In June, 1939, shortly after the start of a two months' concentrated effort in this direction, one of the stock cultures overgrew its associated bacteria and thus purified itself. We have no knowledge of the peculiar conditions which produced this result and consequently have been unable to repeat the purification on other strains. The original pure strain has been maintained for the past year on a liver infusion-human serum medium, transfers being necessary every fourth day. Rigid bacteriologic tests by three separate investigators have failed to reveal any evidence of bacterial growth. The media and methods employed will be presented in an appendix.

This strain of trichomonads, originally cultured from a case of human vaginitis, has been tested for human and animal pathogenicity, and certain experiments have been conducted to determine its physiologic behavior. A preliminary report⁴ on the pathogenicity of the pure strain for human beings has already appeared. The present com-

*Read at the Sixty-Fifth Annual meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

TABLE II. NINE WOMEN FROM WHOM TRICHOMONADS WERE RECOVERED AFTER EXPERIMENTAL INOCULATION

CASE	AGE	PH	SMEAR	FOLLOW-UP EXAMINATIONS			SYMPTOMS	SIGNS
				NO.	NEGATIVE	POSITIVE		
1	21	4.62	I	4	2-4-6	20	None	Vaginal discharge and mucosa remained normal.
2	21	5.12	II	3	5	7-12	None	Scant purulent discharge
3	19	4.10	I	6	3-7-18-28	5-10	None	Purulent discharge; slight mucosal reddening persisting after disappearance of protozoa.
4	23	4.59	I	5	3	5-7 10-12	Soreness	Mucopurulent bubbly discharge; diffuse moderate mucosal redness subsiding to normal by twelfth day.
5	30	3.96	I	3	4	7-18	Soreness	Purulent bubbly discharge; vaginal mucosa diffuse dark red. Duration 3 weeks.
6	24	4.04	I	4		4-7-8-9	Chafing	Purulent bubbly discharge; vulva and introitus inflamed.
7 Non-pregnant	19		II	9		5-10-13 16-23-28 30-36-42	Soreness Itching Burning on urination	Early purulent bubbly discharge; slight redness at introitus; vagina normal 4 weeks; on twenty-eighth day mucosa bright red; increased discharge; menses thirtieth to thirty-fifth day; thirty-sixth day exacerbation of symptoms and signs; some improvement forty-second day.
8	21	4.07	I	6	5	7-9-12 14-19	Soreness Itching Burning	Purulent discharge; increasing inflammatory reaction in vagina seventh to fourteenth days; slight improvement by nineteenth day.
9	18	4.31	I	7	2-4	6-17-18 25-30	Persistent chafing	Purulent bubbly copious discharge, slightly blood tinged; patchy mucosal reddening; duration 21 days (delivered); vagina normal on thirtieth day.

against the possibility that a filtrable virus may be involved in the production of the vaginitis in those who were susceptible to inoculation with the protozoa.

Considering the known frequency of trichomonas vaginitis in all groups of women, consideration should be given to the possibility that some of the 20 women in this group were relatively immune to the protozoa because of a previous, natural infection. No data on this possibility are available. Small inoculums and old cultures may also account for some of the failures.

The remaining 9 women (1 nonpregnant and 8 in the last month of pregnancy) were successfully infected with the trichomonads. Preinoculation and follow-up findings are indicated in Table II.

Two of these patients presented no visible vaginal changes, in spite of the fact that the organisms were detected for twenty and twelve days, respectively.

In the third successful case, the protozoa were recovered ten days after the inoculation but had disappeared eight days later. There was slight reddening of the vaginal mucosa and a moderate purulent discharge, but no subjective complaints. The mucosal hyperemia persisted for a few days after the trichomonads had disappeared.

The fourth patient developed a mucopurulent, slightly frothy discharge by the tenth day, when the vaginal walls showed moderate diffuse reddening, and speculum introduction caused considerable discomfort. Two days later, the inflammation had subsided and the discharge was scant and white, in spite of the fact that the protozoa could still be demonstrated.

The fifth patient developed a vaginitis of slowly increasing severity; by the eighteenth day the vaginal walls were of a diffuse dark red color, and there was a moderate, watery, purulent, frothy discharge with some discomfort.

In the sixth successful case, the patient complained of chafing on the fourth day following the inoculation, when she showed moderate inflammation of the inner vulva and introitus, associated with a yellowish, bubbly discharge, which contained abundant trichomonads. Inflammatory changes in the vaginal mucosa were minimal. The changes persisted for several days, when the experiment was interrupted by delivery.

The nonpregnant patient (Case 7) complained of introital and vaginal soreness a few days after the inoculation. There was a scant, purulent, frothy discharge, and slight reddening of the introitus, which persisted with some variation in severity until the twenty-eighth day, when there was burning on urination, itching, soreness, and an increased watery discharge, and the vaginal mucosa became diffusely reddened. Menstruation began on the thirtieth day and lasted through the thirty-fourth day, with persistence of the urinary symptoms and vulval soreness. Two days after cessation of the menses, there was a definite exacerbation of all the signs and symptoms; the introitus was considerably inflamed; the vaginal mucosa was diffusely hyperemic; there was a moderate, watery, bubbly, purulent discharge; and introduction of a small speculum caused severe pain. One week later, after some spontaneous improvement, treatment was instituted.

The eighth patient revealed inflammatory reddening of the introitus and vaginal mucosa seven days after inoculation. There was a moderate purulent discharge, associated with vulval burning and itching, and increasing introital tenderness. The symptoms and local irritation persisted until she was delivered, nineteen days after introduction of the protozoa.

The ninth woman developed a yellowish, frothy discharge, containing many trichomonads, on the sixth day following inoculation. She was not seen again until ten days later, when there was a complaint of increased vaginal discharge and introital chafing for the preceding week. The vagina contained a copious, watery, bubbly, purulent discharge, which was slightly blood tinged, and the mucous membrane showed numerous ecchymotic patches upon a deeply reddened base. On bed rest, the local condition improved temporarily, but later became aggravated, and persisted until delivery, three weeks after the inoculation. On the ninth post-partum day, there were no complaints and no visible inflammatory reaction, although the trichomonads could still be demonstrated.

Intracranial inoculations in guinea pigs and rabbits were ineffective. Attempts to grow the organisms in developing chick embryos gave irregularly positive results, but it was found impossible to effect a prolonged series of transfers to other embryos.

Trichomonas foetus was successfully inoculated into cattle and temporarily into certain of the dog vaginas, but the remaining animals would not support the protozoa. Human inoculations with this species were not made, but it may be significant that several attempts to infect the vaginas of *Macacus rhesus* monkeys were unsuccessful, even though it was relatively easy to establish the *T. vaginalis* in this environment. The *T. foetus* was grown easily in chick embryos; this confirms Nelson's⁹ report.

In addition to the obvious differences in the behavior of the two strains on animal inoculation, there are definite morphologic and cultural differences which argue strongly against any possibility of transmutation even under environmental changes. *Trichomonas foetus* has only three anterior flagella, while *Trichomonas vaginalis* has four. Moreover, there are essential differences in temperature resistance and media requirements which are well recognized and constitute important protozoologic criteria.

PHYSIOLOGY

A study of the physiologic behavior of *T. vaginalis* is now under way in cooperation with Garth Johnson of the Department of Zoology.

The data already collected have established an optimum growth range of pH 5.6 to 5.9 and have demonstrated that the greatest number of living organisms as determined by hemocytometer counts is present on the fourth day. At this optimum growth range, the average size of the protozoa as determined by A. Kupferberg is smaller than under less favorable pH conditions. Assuming that the size of the cells depends largely upon the rate of division the two observations correlate closely. On the other hand, deviation in either direction from the optimum pH results in decreased growth until division practically ceases at about pH 7.7 and 4.8.

The addition of dextrose markedly stimulates growth and increases the production of gas. Although the organisms grow well under "aerobic" conditions, anaerobiosis favors increased multiplication.

It may be significant that these observations on the growth of a pure culture in vitro correlate with conditions in the human vagina in cases of natural infection. The vaginal secretion in the majority of cases of trichomonas vaginitis is in the neighborhood of pH 5.5 to 6.0. The human inoculations here recorded indicate that a vaginal acidity well below pH 5.5 will not prevent the implantation of the protozoa, but it may be that the lessened acidity in natural infections is the result of the outpouring of alkaline fluid and cellular inflammatory products. This shift in pH creates in turn an even more favorable environment for the further development of the trichomonads.

The vaginal discharge is known to contain glycogen and its decomposition products, a situation which should encourage the growth of

During the height of the local reaction following inoculation, smears from five of the nine successful cases showed no essential change in the vaginal flora, except that the leucocytic elements were increased. Moreover, cultures for hemolytic streptococci, staphylococci, and colon bacilli were negative in the 6 of the 9 patients from whom cultures were made.

COMMENT

The nine successful inoculations, with the development of the clinical picture of trichomonas vaginitis in 5 women of the group, indicate that the local irritation and discharge are due to the protozoa. The possibility of successful implantation apparently does not depend upon the type or acidity of the prevailing discharge, but rather upon such factors as the quantity of the inoculum, the virulence of the protozoa, and the susceptibility of the host. Failure to identify the "*Streptococcus subacidus*"* in the successful cases indicates that these organisms are not essential to the development of vaginal irritation. At the same time, these results should not be interpreted to mean that the altered bacterial flora commonly associated with the protozoa in clinical trichomonas vaginitis does not influence the extent of the reaction, for such organisms might logically be assumed to aggravate the inflammatory process. Furthermore, it is reasonable to assume that certain vaginitides are of bacterial origin, with the protozoan parasites of secondary importance.

The discharge which developed in the successfully inoculated women presented the frothy character so frequently viewed as pathognomonic. It may be significant that pure cultures produce considerable gas from the carbohydrate of the culture media employed. Conceivably the frothiness of the discharge can be attributed to the reaction of the protozoa upon the carbohydrate available in the vaginal discharge, although the possibility of bacterial action cannot be eliminated.

ANIMAL PATHOGENICITY

With the cooperation of Dr. S. H. McNutt, of the Veterinary Research Institute, Iowa State College, an extensive series of animal inoculations has been made, using the pure culture of *Trichomonas vaginalis* here described, and the Glaser-Coria^s pure culture of *T. foetus*, the bovine vaginal protozoon. These experiments will be reported in detail elsewhere, but are summarized here because they offer some evidence to refute the contention that the lower animals may be a source of human infection.

The pure culture of *T. vaginalis* could not be implanted successfully in the vaginas of cattle, sheep, swine, goats, horses, guinea pigs, rabbits, cats, or dogs; but could be maintained in *Macacus rhesus* monkeys, even though no irritation resulted. Oral inoculations in chickens, turkeys, and pigeons were unsuccessful, while rectal instillations in chickens and turkeys gave negative results. Guinea pigs, mice, and turkeys were inoculated intraperitoneally, and cattle, dogs, and rabbits were given intravenous injections of the pure culture without any apparent results.

*A culture of this organism has been available for study through the kindness of the Eli Lilly Company.

REFERENCES

- (1) *Donne, A.*: Compt. rend. Acad. d. sc. 3: 385, 1836. (2) *Hochne, O.*: Zentralbl. f. Gynäk. 40: 4, 1916. (3) *Hibbert, G. F., and Falls, F. H.*: AM. J. OBST. & GYNEC. 36: 219, 1938. (4) *Trussell, R. E.*: J. Iowa M. Soc. 30: 66, 1940. (5) *Trussell, R. E., and MacDougal, R. F.*: AM. J. OBST. & GYNEC. 39: 77, 1940. (6) *Carpenter, C. M.*: Recommended Methods for the Laboratory Diagnosis of Gonococcal Infections, Am. Pub. Health Assn. Year Book, pp. 125-134, March, 1937. (7) *Stein, I. F., and Cope, E. J.*: AM. J. OBST. & GYNEC. 22: 368, 1931. (8) *Glaser, R. W., and Coria, N. A.*: Am. J. Hyg. 22: 221, 1935. (9) *Nelson, P. M.*: Proc. Soc. Exper. Biol. & Med. 39: 258, 1938. (10) *Tucker, W. W., Trussell, R. E., and Plass, E. D.*: AM. J. OBST. & GYNEC. 38: 1055, 1939.

DISCUSSION

DR. GRANDISON D. ROYSTON, St. Louis, Mo.—Dr. Plass suggests the possibility that some of the 20 women in whom trichomonads could not be experimentally implanted may have acquired a relative immunity. Our clinical experience on the other hand seems to show that previous infection confers no such immunity.

Presumably pregnant women were largely used for this experiment because of their greater local resistance to infection. With the statement that the optimum growth range of the organisms is a pH 5.6 to 5.9, I fully agree, and with the statement that a vaginal pH well below 5.5 will not prevent the implantation of the organisms I also agree. It is known that perhaps 5 per cent of trichomonads will not respond to a pH control, but these particular trichomonads are nearly always in a state of symbiosis with some other organism or organisms. In this presentation, there were seven instances in which no associated organisms could be demonstrated.

Roblee of the Washington University Clinic feels that maintaining the acid base balance over a period of two to four weeks determines the ability or inability of trichomonads to persist in the vagina. This maintenance of acid base balance is a normal result of endocrine influence, and the pH balance determines the organisms present. A pH favorable for cure is maintained by inserting into the vagina a No. 11 veterinarian capsule with 80 per cent anhydrous beta lactose, and 20 per cent boric acid, often enough to favor the growth of the Doederlein bacilli. Usually one capsule inserted at bedtime is ordered when treatment is begun, and the intervals lengthened as the discharge diminishes, but repeated often enough to keep some of the powder constantly present in the vagina until a cure is effected.

I should like to ask Dr. Plass two questions: First, have the organisms in his study been cultured successfully for two or more weeks in a pH 4 to 4.5? Second, have the implants persisted in the vagina with the environment controlled to a pH 4 to 4.5 over a period of two weeks' time?

DR. PLASS (closing).—The use of pregnant women in this series was determined entirely by their availability, since we have a large ante-partum group. We also naturally have given thought to the possibility of endocrine influences, and I inferred that when I mentioned environment.

Dr. Royston's questions about the maintenance of a reduced pH on the organisms in the vagina can be answered only partially. We believe that decrease of the pH to 4.0 would certainly prevent the multiplication of the organisms, either in the vagina or in test tubes. We have not, however, followed the changes in pH in the vaginas of these infected women.

The experimental work has been done largely by Mr. Ray Trussell, a third-year medical student.

the protozoa in view of the growth-stimulating action of dextrose in the pure cultures.

A third factor which probably favors the development of the trichomonads is that conditions within the vagina approach the anaerobic, especially in the fornices.

CONCLUSION

Trichomonas vaginalis can produce abnormal discharge and vaginal irritation in women irrespective of the associated bacterial flora or the degree of acidity present.

APPENDIX A

The medium used for maintenance of the pure culture of trichomonads consists of liver infusion agar slants (Difco) (autoclaved) covered with 5 per cent human serum in Ringer's solution (sterilized by filtration). The Ringer's solution contains NaCl 0.6 per cent, KCl 0.01 per cent, CaCl_2 0.01 per cent, and NaHCO_3 0.01 per cent. Heavier growth is favored by adjustment of the reaction to about pH 5.8 and also by the addition of 0.2 per cent dextrose. Transfers of 0.2 c.c. are made with pipettes every three to four days from the sediment at the bottom of the tube.

APPENDIX B

Cultures for bacterial sterility of the trichomonas have been made by us as follows: One drop of the trichomonas suspension on or in each of the following media in duplicate blood agar plates, endo agar plates, 5 per cent human serum in Locke's solution over placenta agar slants, meat infusion agar slants, plain agar slants, dextrin serum water, dextrose serum water, Russel's agar slants, dextrose meat infusion broth, bile peptone broth, chocolate agar slants, hormone agar, gelatin, blood agar slants, brain broth, and Sabouraud's agar. One set was incubated aerobically and the other anaerobically in a McIntosh and Fildes anaerobic apparatus, at 37°C. for eleven days. No bacterial growth could be demonstrated.

The culture of *T. vaginalis* was also submitted to the Department of Bacteriology, which reported as follows: Six tubes each of dextrose meat infusion broth, dextrose meat infusion blood broth, dextrose meat infusion agar, blood agar, chocolate agar, hormone agar, ascitic fluid agar and Sabouraud's agar were inoculated with one drop of the trichomonas culture. Two tubes of each set were then incubated fourteen days at 37°C. under aerobic, anaerobic and 20 per cent carbon dioxide conditions.

"Only one tube (dextrose meat infusion agar slant) had any growth after the two weeks' incubation period. This one tube showed evidence of contamination twenty-four hours after inoculation, and the growth was undoubtedly a contaminant from some outside source.

"These results indicate that the trichomonas culture is apparently free from bacterial contamination."

APPENDIX C

The techniques employed for detection of gonococci, "monilia," and trichomonas in these experiments have been used in this department for several years^{5, 10} with considerable success. The cultural diagnosis of trichomonas has yielded slightly more positive results than has the examination of the fresh vaginal discharge. In this study, however, both methods were employed in the majority of the examinations.

APPRECIATION.—We wish to acknowledge the kindness of Mr. Pelczar and Dr. Porter (Department of Bacteriology) who tested the trichomonas cultures for contamination. Sincere appreciation is extended to Dr. Theo. Jahn (Department of Zoology) for his generous cooperation and to Dr. R. C. Miller for his assistance in the earlier phases of the human pathogenicity experiments.

iliopectineal lines, laterally by the iliopectineal lines, and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. It should be noted that this plane is not that of the anatomic superior strait, but rests slightly below this. The useful diameters of this plane are: (1) anteroposterior, (2) transverse, and (3) posterior sagittal.

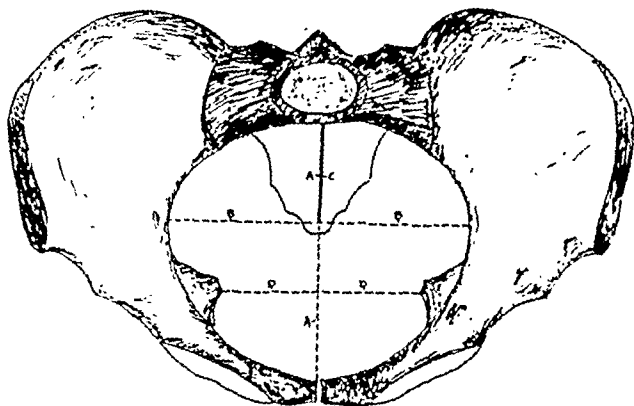


Fig. 1.—The plane of the pelvic inlet. A, anteroposterior diameter; B, transverse diameter; C, posterior sagittal diameter; D, transverse of midplane, see text. (From Am. J. Roentgenol. 44: 9, 1940.)

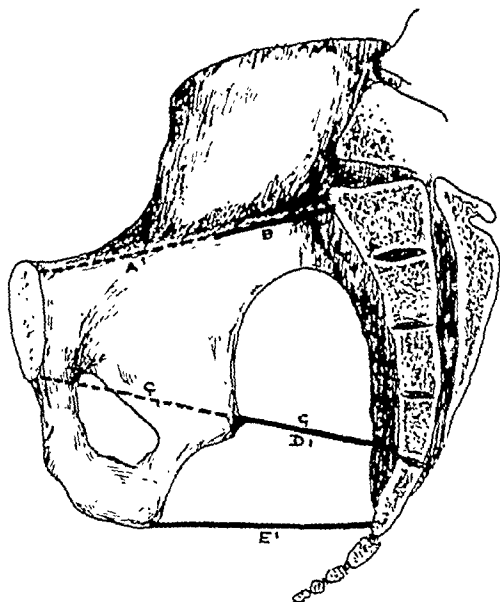


Fig. 2.—Anteroposterior pelvic diameters seen in lateral aspect. A, anteroposterior diameter of inlet; B, posterior sagittal diameter of inlet; C, anteroposterior diameter of midplane; D, posterior sagittal diameter of midplane; E, posterior sagittal diameter of outlet. (From Am. J. Roentgenol. 44: 9, 1940.)

1. The *anteroposterior diameter* of the pelvic inlet extends from a point on the upper posterior surface of the symphysis about 1 cm. from the superior border, posteriorly to the anterior surface of the first sacral vertebra at the point where the iliopectineal lines would meet if they were to be continued. (This point of convergence may or may not be located at the sacral promontory. It is usually somewhat below this eminence.)

ROENTGEN PELVIMETRY AS A ROUTINE PRENATAL PROCEDURE*

HERBERT THOMS, M.D., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University
School of Medicine)

DURING the past six years a roentgenometric survey of the pelvis has been performed on every primigravid woman who has presented herself prenatally for delivery in the wards of the New Haven Hospital. The results have amply proved the value of the procedure and the recent prediction by J. M. M. Kerr that such investigation will eventually become an essential part of prenatal care seems definitely justified.

Many methods for a roentgen survey of the pelvis have been devised. Some of these are not only complicated and require expensive equipment but considerable experience is required in order to secure satisfactory results. It seems obvious that any method which may become usefully adaptable in such a universal field as that of obstetrics must be of reasonable simplicity, of ready interpretation, and of low expense. Such a method is that used in our clinic and one which has been developed through an experience of nearly a score of years. This method employs two films, depicting two views of the pelvis: an inlet view and a lateral view. It is my conviction that for routine purposes the information secured from these two films together with that obtained by certain manual methods offers an excellent survey of the bony pelvis for routine obstetric purposes. Such a survey embraces the measurement of certain pelvic diameters and the evaluation of certain pelvic contours. In order that these important diameters may be easily comprehended we may divide the pelvis into three portions. These are:

1. The plane of the pelvic inlet
2. The midpelvic plane
3. The planes of the pelvic outlet

A knowledge of the contours and of certain diameters of these planes gives not only a concept of the architecture of a given pelvis but will furnish an excellent index as to the available space present in the bony birth canal. I have described these planes and their diameters as follows:¹

The Plane of the Pelvic Inlet.—(See Figs. 1 and 2.) From the obstetric point of view, this plane is bounded anteriorly by the posterior upper surface of the symphysis pubis and the forward portions of the

*Description of a moving picture film presented at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Quebec, Canada, June 17 to 19, 1940.

Planes of the Outlet.—(See Fig. 3.) The third portion of the pelvis of definite obstetric significance is the pelvic outlet. This is in reality two planes, represented by two triangles, the bases of which join each other along the line of the bituberal diameter. The anterior triangle is bounded by the bones forming the pubic arch, the shape of which is of considerable obstetric significance. The two diameters of particular significance are the transverse of the outlet or bituberal diameter, and the posterior sagittal. This latter diameter extends from a midpoint on the bituberal diameter posteriorly to the tip of the sacrum.

In addition to the above diameters, which are of great usefulness in determining pelvic capacity, we should mention certain pelvic contours which are also of importance. The shape of the pelvic inlet, the vertical and lateral contours of the anterior sacral surface, the shape of the sacrosciatic notch, the convergence of the pelvic side walls and the prominence of the ischial spines, and the character of the pubic arch are all considerations which should be taken into account.

To recapitulate, we can say that the significant diameters for use in the routine survey of the bony pelvis are:

Pelvic inlet	Anteroposterior Transverse Posterior sagittal
Midpelvic plane	{ Anteroposterior Transverse or bispinous Posterior sagittal
Pelvic outlet	{ Transverse or bituberal Posterior sagittal

The above measurements may be considered the cardinal diameters of the pelvis. All of the above data including the findings of manual examination may be conveniently summarized on the pelvic estimation chart shown in Fig. 4 which is filed with the patient's prenatal record.

PELVIC VARIATIONS

Variations in form of the bony structures of the pelvis show wide distribution. From the studies of W. W. Greulich and myself² it would appear that the description of the normal female pelvis as noted in most modern textbooks requires considerable revision. Our studies have shown that in white women in this country that type which has been previously described as normal based upon the shape of the pelvic inlet probably occurs in less than one-third of women. In order to study pelvic variations it is necessary to make a simple classification into which certain groups may fall. If such a measure is based upon the general shape of the pelvic inlet and the relation of its two principal diameters to each other, a good working classification becomes available. Attempts by other observers to classify pelvises according to sex characters are bound to be confusing, as the intermingling of sex characters is so great that clinical adaptation of such classification becomes of considerable complexity. Moreover, our studies of pelvises in male adults

2. The *transverse diameter* of this plane is the widest transverse distance separating the iliopectineal lines. It bisects the anteroposterior somewhat posterior to its midpoint, dependent upon the shape of the plane of the pelvic inlet.

3. The *posterior sagittal diameter* of the inlet is represented by that portion of the anteroposterior diameter which lies posterior to the point of intersection by the transverse diameter. The length of this diameter is an index of the amount of space in the important upper posterior pelvis and when abnormally shortened usually represents a posterior displacement of the transverse diameter. This displacement may accompany an abnormal convergence of the iliopectineal lines anteriorly, or, in the case of the flat pelvis, be due to a definite anteroposterior shortening of the pelvic inlet. If due to the latter, the discrepancy between the lengths of the anteroposterior and transverse diameters is at once apparent.

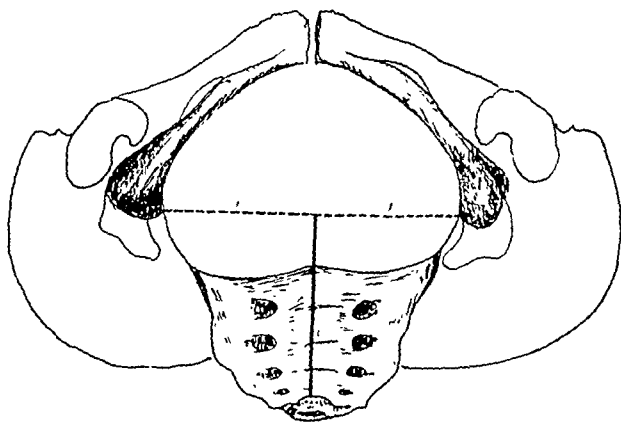


Fig. 3.—The important outlet diameters seen from below. A, transverse diameter; B, posterior sagittal diameter. (From Am. J. Roentgenol. 44: 9, 1940.)

The Midpelvic Plane.—(See Fig. 2.) The second obstetric plane is the midpelvic plane. It is somewhat ovoid in form, large anteriorly and small posteriorly, being narrowed posteriorly by the convergence of the sacrosciatic ligaments. This plane has been defined as being bounded anteriorly by the lower border of the symphysis pubis, laterally by the ischial spines, and posteriorly by the tip of the sacrum. However, these points are not truly in the same plane, for the tip of the sacrum is usually as much as 2 cm. below the level of a line joining the lower border of the symphysis with the bispinous diameter. Therefore, the posterior limit should be placed in the lower third of the sacrum and will usually find itself at the junction of the fourth and fifth sacral segments.

The three diameters which are of obstetric significance in this plane are the transverse or bispinous, the anteroposterior, and the posterior sagittal. This latter diameter, as in the case with the plane of the pelvic inlet, represents that distance on the anteroposterior diameter which lies posterior to the point of intersection by the transverse or bispinous diameter.

diameters which have been described, together with a consideration of the important contours, such as inlet, notch and pubic arch, one can form a fairly adequate estimation of pelvic capacity for obstetric purposes.

It is important to know the chief characteristics of male pelves which which may affect female pelves.

1. The male characteristics which may affect the pelvic inlet are: (a) The inlet is in general more circular. (b) The widest transverse diameter is, therefore, slightly displaced posteriorly. (c) The posterior sagittal diameter is, therefore, relatively shortened.

2. The male characteristics which may affect the midplane are: (a) The narrowing of the pelvic side walls with increase in size and prominence of ischial spines results in a relatively decreased bispinous diameter. (b) Laterally the male type or narrow sacrosciatic notch decreases posterior pelvic capacity in this plane and is manifest in a relatively shortened posterior sagittal diameter.

3. The male characteristics which may affect the pelvic outlet are: (a) Narrowing of the pubic arch with less arcuate formation of its sides and relative shortening of the bituberal diameter. (b) Because of the forward displacement of the sacrum forming the posterior wall of the male notch, the posterior pelvic capacity in this plane is also decreased, which is manifest in a relatively shortened posterior sagittal diameter of the outlet.

Male characters may appear in female pelves at the inlet, the mid-pelvis, or the outlet, and in a certain small group of pelves they may occur in all three portions, the complete male pelvic type. It is obvious that they may have a considerable obstetric significance, particularly in the latter instance.

Some idea of the distribution of these basic pelvic types in white women of the clinic group may be gained from their incidence in 800 primigravidae who were delivered at term (child 2500 Gm. or over) in the New Haven Hospital (Table I).

Again the fact impresses us that 62 per cent of this series present pelves whose inlet is not that described as normal in textbooks of

TABLE I

TYPE	NUMBER	PER CENT
Dolichopellic	129	16.12
Mesatipellic	367	45.88
Brachypellic	272	34.00
Platypellic	32	4.00

TABLE II

TYPE	100 NURSES	582 CLINIC WOMEN	107 CHILDREN
Dolichopellic	37.0	14.5	57.9
Mesatipellic	46.0	44.5	33.6
Brachypellic	17.0	34.3	8.3
Platypellic	----	6.7	

anatomy. In a recent study by Greulich and Thoms of the pelvic inlets in 789 white females, which included 582 clinic women, 100 nurses, and 107 young females from 5 to 15 years, the incidence of pelvic types was

have shown us that in male pelves, also, great variation is found.³ Furthermore, the use of a simple dimensional means as a basis for classification eliminates the disadvantages bound to arise from information based largely on subjective impressions.

We consider, therefore, that in general the pelvic inlet may assume one of four shapes, which may be described as: (1) an anteroposterior oval; (2) a circle; (3) a transverse oval; and (4) an exaggerated trans-

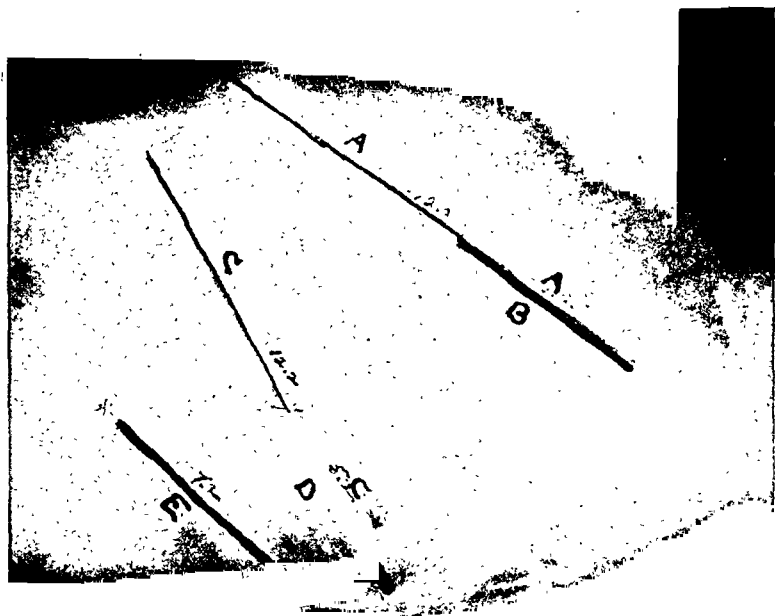


Fig. 4.—Film of lateral pelvis. Lines indicate cardinal diameters. *A*, anteroposterior diameter of inlet. *B*, posterior sagittal diameter of inlet. *C*, anteroposterior diameter of midplane. *D*, posterior sagittal diameter of midplane. *E*, posterior sagittal diameter of outlet. (From *Am. J. Surg.* 39: 56, 1940.)

verse oval. We can further describe this morphology by considering the relation of the anteroposterior and transverse diameters of these figures to each other, and on this basis we may adopt terms for pelvic types which will be useful:

1. Dolichopellic or anthropoid type pelvis. The transverse is less than the anteroposterior diameter.
2. Mesatipellic or round type pelvis. The transverse is equal to, or slightly greater (not more than 1 cm.) than, the anteroposterior diameter.
3. Brachypellic or oval type pelvis. The transverse diameter is more than 1 and less than 3 cm. greater than the anteroposterior diameter.
4. Platypellic or flat type pelvis. The transverse diameter is 3 cm. or more greater than the anteroposterior diameter.

The above classification is useful simply as a basis for description of individual pelves. It is obvious in the individual case that the obstetrician is not so much concerned with the group in which a pelvis may align itself as he is with the measurements and contours which reveal its useful capacity for childbearing. Given the eight cardinal

2. The level of the pelvic inlet above the sensitive film is established as follows: (a) By means of calipers the vertical distance is measured from some point on the table top to a point on the anterior surface of the symphysis pubis 1 cm. below its superior border, or this point in space may also be determined by measuring downward with a tape from some point on the tube stand. (b) By means of calipers the distance is determined from the interspinous space between the fourth and fifth lumbar vertebrae, as determined by palpation, and the table top. For practical purposes, an imaginary line drawn between the posterior point on the body and the point on the upper and anterior surface of the symphysis will bisect the plane of the pelvic inlet.

3. The tube is centered in the midline about 6 cm. posterior to the upper border of the symphysis and the exposure is made.

4. The patient is removed from the table, the tube and exposed film remaining in situ.



Fig. 5.—Film of pelvic inlet. Lines indicate cardinal diameters. A, anteroposterior diameter of inlet. B, posterior sagittal diameter of inlet. C, transverse diameter of inlet. D, transverse diameter of midplane. (From *Am. J. Surg.* 39: 56, 1940.)

5. The centimeter grid, a lead plate with perforations exactly 1 cm. apart, is introduced into the same plane as that previously occupied by the pelvic inlet, as determined by the caliper readings and the measuring tape, and a second (flash) exposure made on the previously exposed film.

In viewing the film an outline of the pelvic inlet is shown (Fig. 5) and any diameters of this plane may be measured, using the dots as a centimeter scale. The interspinous diameter may also be measured in this film, using a correction table for the level at which they rest in the pelvis. This level is determined in the lateral film.

In a recent communication⁵ I have described a simple calibrated calipers for measuring pelvic diameters, thus eliminating the use of the

as indicated in Table II. The incidence of the various types in the student nurses seems especially significant in view of the superior physical status and economic level of the women comprising that group. The data from the younger girls are also of significant interest, showing the high incidence of the dolichopellic type in this group.

ROENTGEN TECHNIQUE FOR PELVIMETRY

The following technique is essentially that described by H. M. Wilson and myself in 1939⁴ and again by myself in 1940.¹

For routine purposes we take two views: One of the pelvic inlet by the so-called grid method, and one lateral projection. It has become obvious to us that an adequate survey of the pelvis for obstetric purposes is not possible without the employment of both techniques. Furthermore, inasmuch as the mensuration of the anteroposterior diameter of the pelvic inlet may be determined in both views, each procedure becomes an excellent check on the accuracy of the other. Our routine is to take the lateral projection first, and this technique may be described as follows:

1. The patient removes her clothing, putting on heelless slippers and the usual hospital bed gown open at the back.

2. She is placed standing in front of an erect Bucky diaphragm or an adjustable cassette changer, such as is used for chest work, with either the right or left lateral aspect of the body toward the target. The arms are folded across the chest.

3. The target film distance is 36 inches and the target is centered at a point on the external conjugate diameter one-third the distance from the symphysis pubis to the depression under the fifth lumbar vertebra.

4. A binder is placed around the patient and attached to the cassette changer to insure further steadiness during the exposure.

5. Before the exposure is made, an upright metal rod (lead and iron) with a centimeter scale perforated in a lead strip is placed posterior to the patient close to the fold of the nates.

6. The time of exposure varies with the thickness of the patient, all other factors being constant; in general the time is from seven to twelve seconds.

Comment on Lateral Technique.—When developed and viewed the following landmarks should be readily identified (Fig. 4): anterior and posterior borders of the symphysis pubis, acetabula, ischial spines, ischial tuberosities, the lower lumbar vertebrae, the promontory and anterior surface of the sacrum, and the sacrosciatic notch. On one edge of the film may be seen the shadows cast by the perforations giving corrected centimeters in the sagittal plane of the patient. By means of calipers, using this scale, any diameters in this plane may be measured.

The advantages of this lateral technique may be summarized as follows:

1. All the anteroposterior diameters of the bony pelvis may be measured, including those of the pelvic inlet, midpelvis, and inferior strait. The anterior and pelvic inlet diameters of the important midpelvic plane are readily determined.

2. The contours of the anterior surface of the sacrum may be studied, a matter of importance in the recognition of sacral abnormalities, especially those due to the influence of rickets.

3. When lateral roentgenograms are made at term or in labor, the relation of the presenting part to the superior strait may be studied with advantage.

The centimeter grid method for pelvic inlet pelvimetry may be described in its essentials as follows:

1. The patient is placed on the roentgenographic table in a semirecumbent position which is maintained by a backrest. In placing the patient in position we endeavor to make the pelvic inlet of the pelvis horizontal.

settled before a standard classification can be accepted. In the future, the worker interested in the study of pelvic morphology must deal with the classification of pelvic shapes which are borderline between the long oval, the round, or the transverse oval. He must attempt to determine the significance of masculine characters.

In recent years considerable emphasis has been placed upon measurements as obtained by methods of roentgen pelvimetry. Unfortunately a roentgen technique devised for pelvimetry purposes may fail to permit visualization of the pelvis

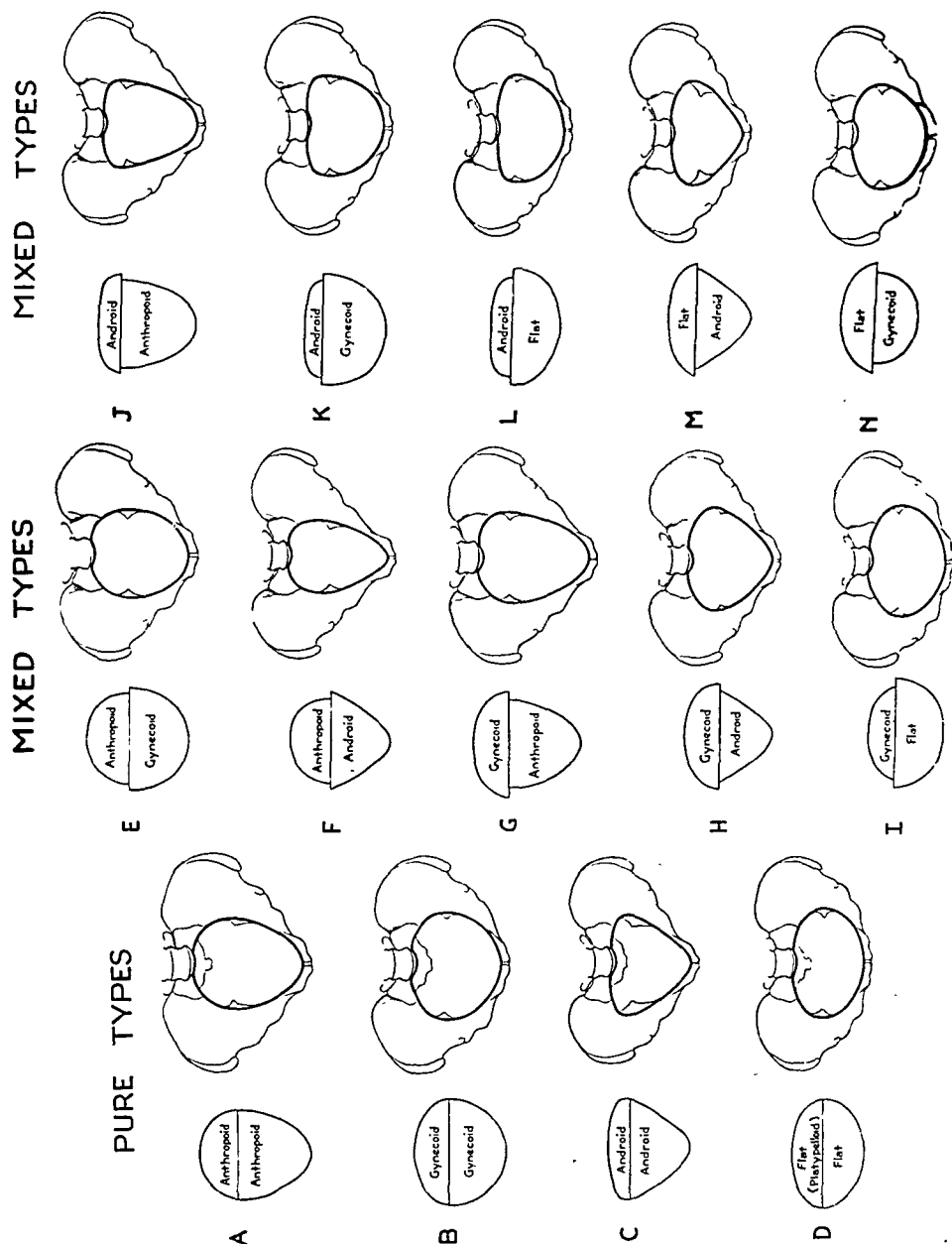


Fig. 1.—The four pure forms present a characteristic inlet shape to the anterior and posterior segments. Mixed types are classified on the principle of the combination of the posterior segment of one pure form with the anterior segment of another. Fourteen types occur; four pure and eight mixed. Anthropoid-flat and flat-anthropoid forms represent impossible theoretical types.

from inlet to outlet. In the use of the flat film technique, the worker should appreciate the possible sources of error in measurement and the effect of distortion upon pelvic shape if errors in technique occur.

Our experience with the method described by Dr. Thoms has been limited. But from experiments on skeletal pelvises, we have found that accurate measurement of the widest transverse diameter of the inlet is dependent upon placing the grid in the plane of the inlet. This correct plane at the widest transverse diameter is usually 2 to 3 cm. below a line joining the promontory and the superior posterior

grid and the upright rod. The general principle, however, remains the same and identical results can be secured by both techniques.

It will be noted that in addition to the important pelvic contours the two films make available seven of the eight cardinal diameters. The intertuberal or transverse diameter of the outlet may be adequately estimated by the usual manual method, thus saving the exposure of an additional film.

With this additional knowledge of pelvic dimensions and pelvic architecture, it is obvious that a great deal of experience must be gained before the proper clinical evaluation may be secured. In a previous communication⁵ I have made such a study based upon the results in 200 primigravidas. This, however, is but a beginning of a study which must be further expanded. One thing seems apparent, that no longer need we be ignorant of the important dimensions of the bony pelvis in any given case, and this knowledge combined with skillful clinical experience will make for better obstetrics.

In conclusion, we must be reminded again that the knowledge of pelvic dimensions and contours is but one part of a complex obstetric picture which must be viewed as a whole for successful prognostication and the skillful conduct of delivery.

The conclusions in this paper were derived from investigations aided by grants from the Clinical Research and Teaching Funds of Yale University School of Medicine.

REFERENCES

- (1) *Thoms, H.*: Am. J. Surg. 3: 691, 1940. (2) *Greulich, W. W., Thoms, H., and Twaddle, R. C.*: J. A. M. A. 112: 485, 1939. (3) *Thoms, H., and Greulich, W. W.*: AM. J. OBST. & GYNEC. 39: 56, 1940. (4) *Thoms, H., and Wilson, H. M.*: Yale J. Biol. & Med. 11: 179, 1939. (5) *Thoms, H.*: Am. J. Roentgenol. 44: 9, 1940.

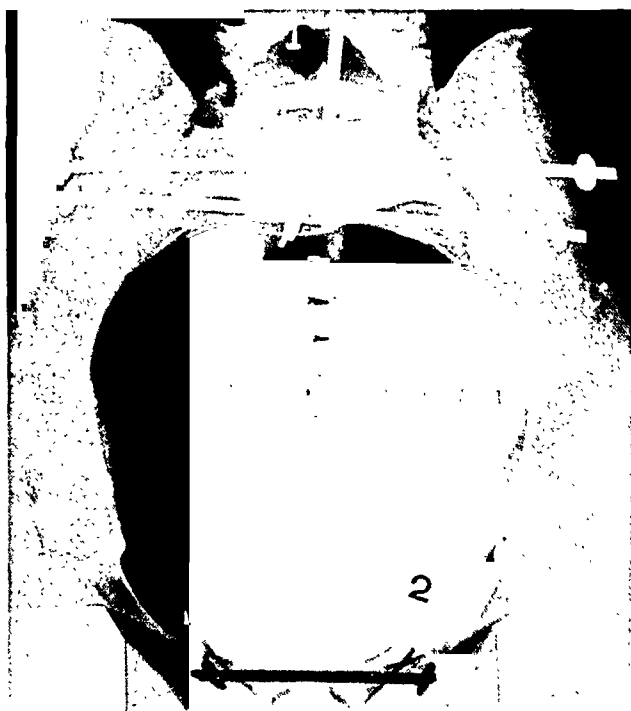
DISCUSSION

DR. HOWARD C. MOLOY, NEW YORK, N. Y. (By Invitation).—Dr. Thoms in his classification recognizes three anatomic forms: the long oval, the round, and the transverse oval. He also recognizes an overlapping of these types. This classification was proposed by Turner in 1885. A fourth group has been added (brachypellic) which may be said to represent an intermediate type between the round form on the one hand, and the transverse oval on the other. In addition to these types, the presence of masculine characteristics must be considered. It is to be observed that two controversial aspects of the question of morphologic classification present themselves. The first deals with the use of three or four classic shapes to illustrate the blending from the longitudinal oval through the round to the transverse oval type. Anthropologists consider that these variations in shape represent normal growth variants and believe that the intermediate types are so numerous that a classification cannot be sufficiently simplified to consist of three or four groups. In our roentgenologic studies we have also been impressed with the frequent occurrence of types which are not exactly a longitudinal oval form, nor are they round in shape. We believe, therefore, that some provision should be made for the classification of these mixed forms. (Fig. 1.)

The second controversial point deals with the so-called masculine type of pelvis. Dr. Thoms provides for this type by advising that masculine characters at the inlet, the midpelvis, and the outlet may be described for each pelvis in addition to the classification as determined by the ratio between the inlet measurements. But extreme masculine forms occur which, in our opinion, should be included as definite types in a formal classification. These two important points must be



A.



B.

Fig. 3.—A, In this skeletal pelvis, the grid was placed between the symphysis and the promontory considerably above the plane of the widest transverse diameter. As a result, the grid records greater distortion than actually exists at the plane of the inlet. Roentgen measurement of widest transverse diameter is 10.8 cm. Actual skeletal measurement of the same diameter is 11.4 cm. Error is 0.6 cm. B, When the grid is placed in the true plane of the inlet, an accurate roentgen measurement results. The grid cannot be placed with precision in the correct inlet plane in the living patient in all instances.

aspect of the symphysis. If by chance the grid is placed above this precise inlet plane, an error in the measurement of the widest transverse diameter may occur. (Figs. 2 and 3.)

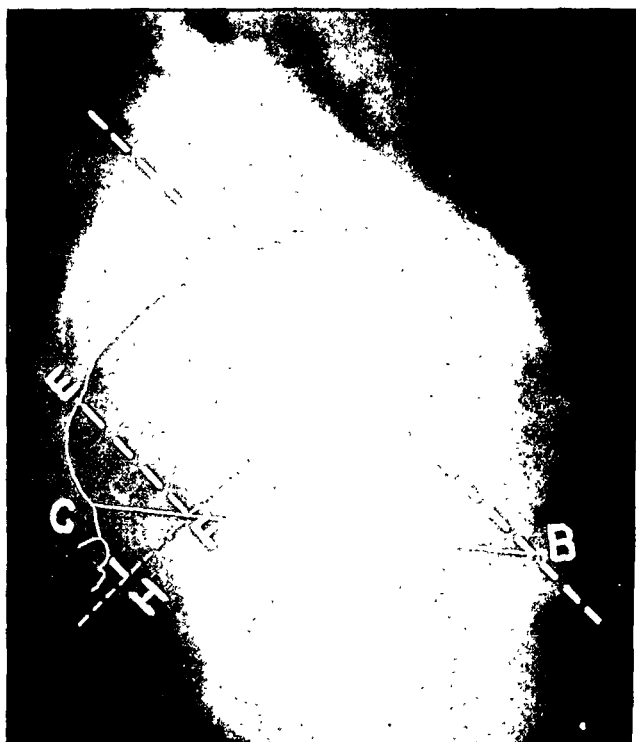
We must realize that with flat films, distortion of the inlet shape occurs when the plane of the inlet is tilted, thereby giving an imperfect inlet view. In Fig. 4 a true inlet view to the left and a slightly sloping view to the right are shown. In the slightly sloping view to the right, the angle of the forepelvis is elevated above the film to a greater degree than regions in the posterior pelvis. As a result the forepelvis is wider and the posterior pelvis is flatter than exists in a more perfect inlet view. By experimentation we have found that the difference in tilt between cases comparable to the two shown in this slide represents approximately twenty degrees. The magnitude of the distortion present in the example to the right, Fig. 4, *B*, in our opinion, should preclude tracing of this inlet for use as an index of its shape. For this reason we believe stereoroentgenograms are more satisfactory than flat films in the interpretation of pelvic morphology and the fetal pelvic relationship.



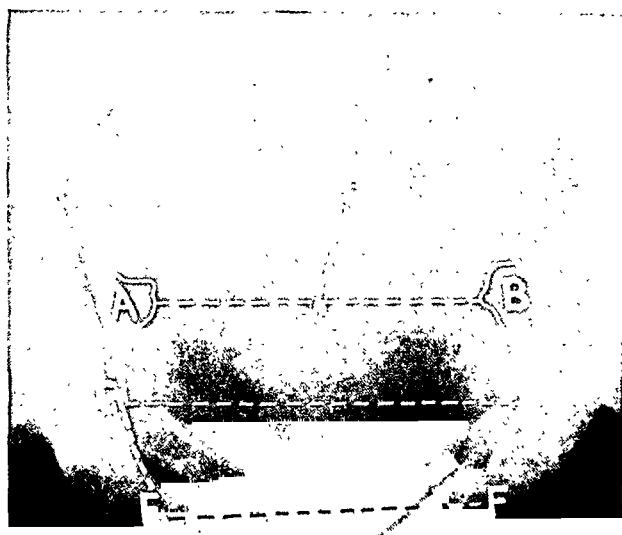
Fig. 2.—When the plane of the grid is situated on a line joining the symphysis and promontory, the grid is considerably above the plane of the widest transverse diameter of the inlet. This causes more distortion in the grid than exists at the plane of the inlet, and an error in the widest transverse diameter occurs (see also Fig. 3).

The lateral roentgenogram supplies a method of measurement of the true conjugate diameter and at the same time gives information regarding the inclination and curvature of the sacrum. The most significant anatomic observations to be made from the lateral roentgenograms are those relating to the posterior pelvis, especially in regard to relationship of the lower sacrum to the ischial spines. The manner in which a forward sacrum may decrease pelvic capacity behind and below the ischial spines can be seen at a glance without complicated methods of analysis. A simple method which we have found very useful is shown in Fig. 5, *A*. Observe the length of the posterior sagittal diameter behind the spines and the parallel relationship to the plane of the inlet, the same plane previously referred to in the placement of the grid for accurate measurement of the widest transverse diameter. The forward encroachment of the sacral tip and the level of the sacrococcygeal platform to the ischial spine are clearly evident.

Hodges, Ball, Snow, and others have offered their own method for analysis of the lateral roentgenogram. These workers have used one common principle. This refers to lines drawn from the top of the symphysis at a tangent downward and backward to the sacral tip and to the lower sacral region through the ischial spines.



A.



B.

Fig. 5.—A, Lateral analysis: *AB*, plane of inlet. *BC*, Tangent line from top of symphysis to lower sacral region. *EF*, Posterior sagittal at level of ischial spines. *FH*, Level of sacrococcygeal platform to the ischial spines.

B, The intertuberous diameter is more correctly considered as the widest transverse diameter of the outlet *CD*. The convergence of the side walls toward the lower aspects of the pubic rami does not denote the origin of the widest transverse diameter of the outlet, but rather a line which passes transversely across a small segment of the outlet *EF*. The interspinous diameter *AB* is always smaller than the widest transverse diameter of the outlet.

The anteroposterior diameter of the midplane as defined by Thoms slopes downward and backward from the under surface of the symphysis to the junction between the fourth and fifth sacral segments. Fig. 5, *A* shows that the length of these lines, especially when drawn from the top of the symphysis to the sacral tip, is not at all significant inasmuch as the head, in the mechanism of labor, has



Fig. 4, *A*.



Fig. 4, *B*.

A SIMPLE METHOD OF MAKING AN ARTIFICIAL VAGINA*

FREDERICK H. FALLS, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Illinois College of Medicine)

THE operative creation of a normal vagina is impossible. The creation of an epithelial-lined tube which may be used for normal cohabitation is not only possible, but is a relatively simple procedure. Its successful accomplishment depends on a knowledge of anatomy and some experience in gynecologic plastic surgery. One of the great difficulties in developing an adequate technique for the performance of this operation is the lack of suitable clinical material on which to base technical experience. Many operators of considerable gynecologic experience have seen only one or two cases. Therefore it follows that no one operator has had sufficient personal experience with the various operations proposed to be able to express an opinion regarding their comparative merits and disadvantages.

The indication for the operation may be open to some difference of opinion. Primarily it should be undertaken purely as a means of providing for cohabitation in women presenting this defect who are married or contemplate matrimony. It would also seem reasonable to defer operation in all cases until the patient was about to be married so that the act of coitus would preserve the patency of the artificially prepared tube. Dannreuther¹ has suggested that estrin should be present in the blood, that the patient should be young and attractive and have a normal sex urge. There is another factor which should be kept in mind which we feel is more important in some cases than in others. There is a natural inferiority complex in some of these patients, because of the knowledge of the abnormality; and this may be greatly lessened if an attempt is made to form an artificial vagina, even if the attempt is not entirely satisfactory from an anatomic standpoint, and even though they fail to menstruate subsequently.

The embryologic development of the vagina is not entirely clear and accepted by various authorities in this field. Koff² has summarized the various views, and we believe that the one that best fits the clinical findings in patients presenting absence or deformity of the vagina is as follows:

The lower one-third of the vaginal tube develops from the sinovaginal bulbs (urogenital sinus) and the upper two-thirds from the caudal portion of the uterovaginal canal (Müllerian ducts). Clinically we see some patients who have a total absence of the upper two-thirds of the vagina and still present a shallow pouch which represents the rudimentary lower one-third. Other patients present an entire absence of the vaginal tube. Apparently the upper two-thirds never develops independently of the lower one-third. It is an important fact that in a large

*Read, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seignior Club, Que., June 17 to 19, 1940.

long since passed below the symphysis before the obstruction offered by the lower sacral region is encountered. Therefore, from the obstetric standpoint, the length of the posterior sagittal at the level of the spines, and its level with respect to the sacral tip, shows at once the degree of encroachment of the sacrum on the lower pelvis. Available outlet space is determined by the length of diameters extending parallel from points on the lower pubic rami to the lower sacrum rather than by lines from the top of the symphysis to the lower sacrum.

Finally, somewhat similar remarks may be made in reference to the intertuberos diameter. Dr. Thoms advises clinical methods for measurement. Ball and Snow in recent publications have chosen a point where the line of the side walls intersects the lower pubic rami as the intertuberos diameter. As shown in Fig. 5, *B*, this diameter as described by them is actually shorter than the interspinous diameter in many instances, and this gives an erroneous index of the width of the outlet. The intertuberos diameter from the roentgenologic and clinical standpoint has not been defined with accuracy, because it is difficult to pick out the significant anatomic point of origin of this important diameter. As the pelvic view shown in Fig. 5, *B* indicates, the significant transverse diameter at the outlet is the "widest" diameter in the lower forepelvis. This diameter does not originate from any specific location on the tuberosities of the ischium, because this widest diameter varies with the character of the base of the ischial spines behind and in front with the inward curvature of the pubic rami. This diameter may be termed the "widest transverse diameter of the outlet."

I regret that time does not permit a detailed description of the various observations made in arriving at the conclusions mentioned in this discussion. The pioneer work of Dr. Thoms in roentgen pelvimetry has been appreciated by our specialty for many years.

Counsellor¹⁵ and Babcock¹⁶ working independently have used Thiersch's grafts cut from the inner thigh and sewed around a glass tube with the skin side next to the tube. A tunnel was made sufficiently deep between the bladder and rectum and the tube introduced and held in place for a week. The canal was kept open by passing a well-lubricated glass tube daily.

In the opinion of most observers, including the writer, the methods using the bowel, either ileum or rectum, are potentially too dangerous in the hands of the average gynecologic surgeon and have other objections that render them not the first choice for a given case.

The Frank-Geist operation necessitates prolonged hospitalization (ten weeks) which may be an insurmountable financial barrier to some patients.

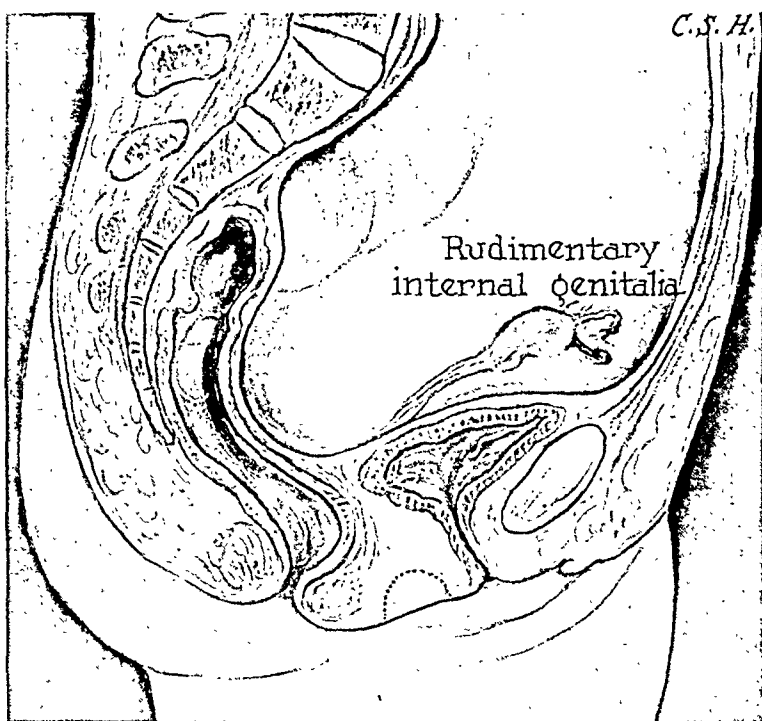


Fig. 1.—Anatomy of congenital vaginal defects.

The Graves method is open to two main objections: First, that hair growth may occur on the inverted flaps; Second, if sloughing occurs, the operation cannot be easily repeated. There is also undesirable distortion and mutilation of the vulva.

OPERATIVE TECHNIQUE

The operation here described is extremely simple, devoid of dangers and gives satisfactory results in the cases in which it has been used. As a rule in these patients, the external genitalia are fairly well formed, and in many there is a slight pouch or at least a dimple in the perineum to indicate the normal location of the vagina. A circular incision is made around the edges of this dimple, creating a disk about 2 to 3 cm. in diameter. The edges of this disk are undercut, leaving the center attached to the underlying tissue. The loose connective tissue between the bladder and rectum is separated by blunt dissection, and the disk of skin is pushed inward to form the vault of the new vagina. Skin flaps about 1 cm. wide

proportion of these women the uterus, tubes, and ovaries are very rudimentary or may be absent in whole or in part.

The first attempt to create an artificial vagina which we were able to find was by Dupuytren,³ in 1817, which consisted of making an opening between the rectum and vagina and inserting tampons to maintain patency while epithelization was occurring. This method was not very successful.

Mackenrodt,⁴ in 1911, formed a similar tunnel and transplanted vaginal mucous membrane from another patient. The result of this procedure was unsatisfactory.

Baldwin,⁵ in 1907, excised a ten-inch loop of ileum and united the ends of the remaining bowel by end-to-end anastomosis. He then tunneled between the bladder and rectum and pulled the middle of the excised loop downward; and after opening it, he sewed the edges to the skin of the perineum. This left a mucous membrane-lined cavity which did not shrink and whose walls were smooth and non-irritating. The obvious objection was the danger involved, and that following ingestion of food an irritating secretion from the vagina was noted in some of these cases.

Schubert,⁶ in 1911, described a method involving the use of the bowel which depends on freeing the lower six inches of the rectum, transposing it forward to a new opening on the perineum where the vulval opening should be, and drawing down the upper end of the bowel to the anal opening. This implies the removal of a considerable portion of the coccyx to expose the rectum, and there is considerable danger of infection following operation, and damage to the function of the sphincter ani.

In 1927, Frank and Geist⁷ made a tubular graft from the inner surface of the thigh with a base near the vulva. Three weeks later this was freed at its distal end, opened, and sutured over a rubber plug with the epithelial surface next to the plug. By blunt dissection a cavity was created between the bladder and rectum, and into this the plug with its epithelial covering was fitted, bringing the subcutaneous fat surface of the graft into approximation with the raw surface of the canal. The rubber plug was removed in eight days and in two weeks the graft was healed in place.

Graves⁸ has suggested the creation of a blind pouch by blunt dissection between the bladder and rectum and the formation of a lining for the same by using epithelial strips cut from the labia minora and the sides of the vulva, and sewed over a glass model bringing their free edges together. The model is removed and the pouch is then inverted into the cavity, and held in place by a glass cylinder until attachment is established.

Wharton⁹ describes a technique similar to that by Meigs in which he used a condom filled with paraffin as the vaginal plug after creation of a space between bladder and rectum by blunt dissection. He reports four successful cases by this method. He stresses the importance of the proliferatory power of the vaginal epithelium in lining the cavity thus created and feels that the operation might not be successful in cases where there was no evidence of beginning vaginal formation before operation.

Masson¹⁰ has been the chief sponsor of the Baldwin operation in this country, having published five cases in 1932 without a death and with good functional results.

Judin¹¹ reported six cases without mortality, using the Baldwin technique, and is an enthusiastic advocate of the procedure. He admits however a mortality of 10 per cent in a group of cases done in Russia by surgeons who reported their results to him personally, and a mortality rate of 14.1 per cent in a series of 105 cases collected by Rabinovitch.¹² He points out also that in a series of 61 cases of the Popov-Schubert operation a mortality of 4, or 6.6 per cent, is reported.

Emil Novak¹³ in a personal communication reported five cases done by the Baldwin method without mortality.

Meigs,¹⁴ in 1938, described a procedure that seems very simple if practical. He tunneled between the vagina and rectum, inserted a pyrex glass tube and held it in place with a "T" binder, later doing a skin graft to bring the skin of the vulva up to the epithelium-lined pouch thus formed. He reported only one case which was successful, although there was difficulty in keeping the tube in place and preventing infection.

by catgut sutures. The raw surface of the flap comes in contact with the walls of the cavity formed to permit sinking the disk, and the blood supply is established between the two. The flaps also get a good blood supply through their attached pedicle. Epithelization occurs between these transplanted strips of mucosa, and in about two weeks a completely epithelized tube is formed. During healing, the pouch is packed with gauze daily, and a moderate amount of pressure is maintained.

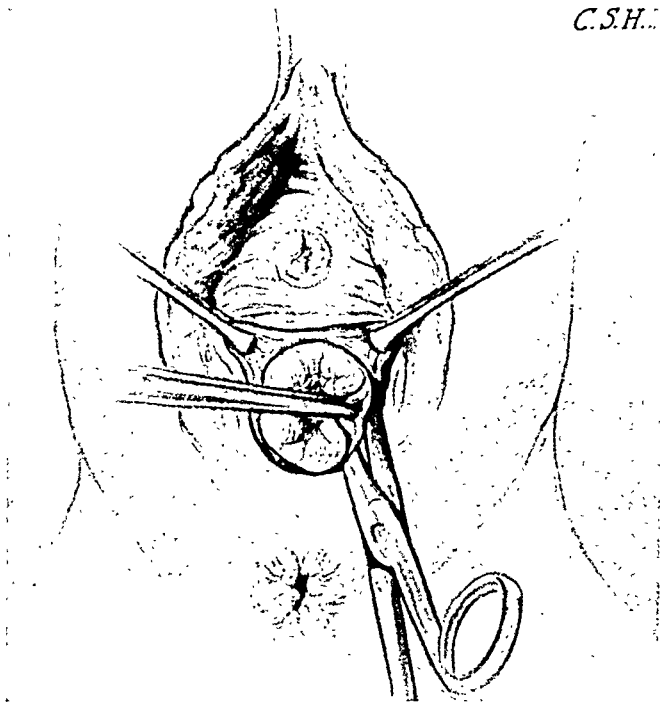
C.S.H.

Fig. 4.—Freeing edges of vaginal pouch.

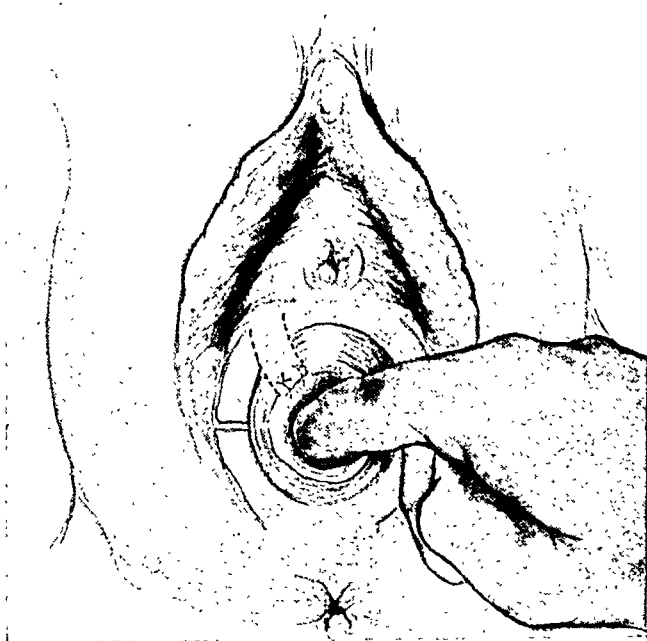
C.S.H.

Fig. 5.—Sinking pouch and flap formation.

are cut from the edges of the vulval opening by making lateral cuts at 3 and 9 o'clock, the width of the flap, and extending the incision upward and downward for about 2 to 3 cm., making two ribbons attached to the side of the vulva at one end which can be swung into the cavity, and the free edge sewed to the edges of the disk, forming the vault of the new vagina. The same is done on the opposite side so that we have four strips of vulval mucosa 1 cm. wide, each attached externally to the edge of the vulva and internally sewed to the disk forming the vaginal vault

C.S.H.

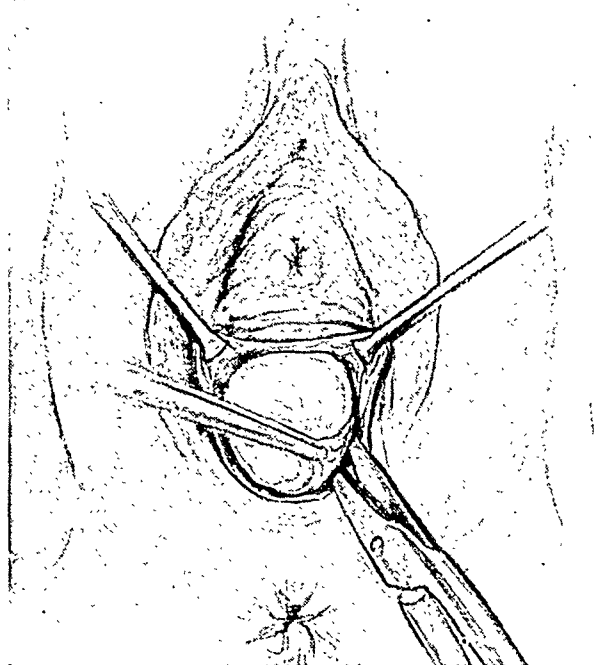


Fig. 2.—Dissection between bladder and rectum.

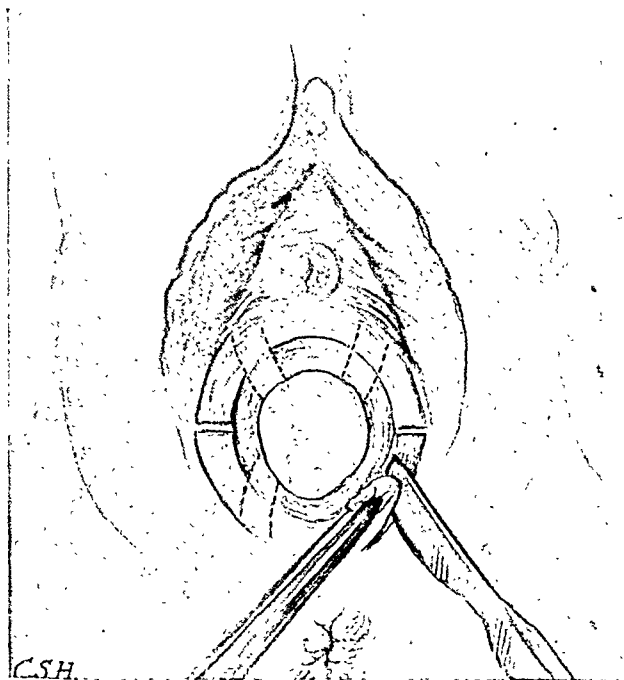


Fig. 3.—Dissection of flaps after freeing disk.

the bladder and rectum following with blunt dissection until on advancing the needle I aspirated urine and knew that I had penetrated the bladder. I then enlarged the tract so that it admitted the tips of two fingers, the whole pouch being about three inches deep. Thinking I might be able to connect with this pouch by downward dissection from above, I opened the abdomen and found no uterus, tubes, or ovaries in the normal position. I was about to close the abdomen when at the left inguinal ring I noticed a small uterus 1 cm. long by 0.5 cm. wide with a rudimentary left tube and ovary. I clamped the pedicle at the ring and removed the specimen. Postoperatively I packed the vaginal pouch and had the patient dilate it with a test tube daily. Epithelization occurred and a satisfactory vaginal tube four inches deep resulted.

CASE 2.—In 1926, a 27-year-old married colored woman entered the Cook County Hospital at Chicago, complaining of monthly cramps in the lower abdomen. The abdomen showed no tumor masses or tender areas. The vagina was absent. The external genitalia were fairly well developed. On rectal examination a mass about as large as a cervix could be felt at about the location of a normal cervix. I cut in between the rectum and bladder, making a tunnel about three inches deep, but could not reach the nodule. I therefore opened the abdomen suprapubically and found a rudimentary bicornuate uterus didelphus with a fibroid about 2 cm. in diameter on each cornu. A fibrous strand connected the lower end of these structures to the region between the rectum and bladder where the vagina should have been. The uterine corpora were about 3 cm. long. I had mistaken one of the fibroids for a cervix. I attempted to produce a vaginal pouch by packing the tunnel I had made with gauze. The patient left the hospital and could not be traced thereafter, so that the ultimate success of the operation is in doubt. An interesting fact in these cases is the "dysmenorrhea" which each of these patients complained of in spite of the fact that there was no evidence of blood retention and most rudimentary internal genitalia.

CASE 3.—On Jan. 18, 1934, a 25-year-old married white woman presented herself, who had at the age of eleven noted some vaginal bleeding one night, and never experienced this again. She complained of dysmenorrhea on a few occasions that might have corresponded to times she would have been menstruating. She came to the clinic because she wanted to become pregnant and had never menstruated. Physical examination revealed no marked anomaly except that the vagina was very shallow, $1\frac{1}{2}$ to 2 inches long, and the uterus including the cervix and adnexa were not palpable. She was operated upon by the method here described and a normally appearing six-inch vaginal tube was produced.

CASE 4.—E. L., aged 27 years, office clerk, had congenital absence of vagina. She had consulted three physicians when 16 because of failure to menstruate. She was given pills but not examined. She paid no further attention to the condition until at the age of 21 she experienced abdominal cramps while at work. The company physician examined her, made the diagnosis and referred her to a specialist who recommended operation when she wanted it. She came to our out-patient department five years later when she contemplated marriage. Not even a rudimentary pouch was present. She was operated upon on Nov. 25, 1936, for the first step of our operation, and the second step on April 15, 1937. Following this operation a pouch five inches long which admitted two fingers snugly was created.

CASE 5.—A rather unusual patient presented herself at the Cook County Hospital in April, 1937. There was a rather shallow pouch about three inches deep which was partially prolapsed. The woman was a widow and had had sex relations for several years but had neither menstruated nor conceived. On examination, the vagina was represented by a blind pouch. The uterus could not be palpated and there were some tumor masses in the region of the ovaries. It was decided to attempt a suspension of the vaginal pouch. The abdomen was opened and a rudimentary uterus with atrophic tubes and ovaries was found. The masses previously mentioned proved to be multiple fibroids of the round ligaments up to 4 or 5 cm. in diameter. The vaginal vault was suspended as well as possible with the

After healing is complete, the pouch will be found to be about two inches deep, and may be deepened by wearing a vaginal plug at night and making rather strong pressure on the disk or vaginal vault daily. The patient can be taught to do this herself.

In cases in which a rudimentary pouch is present to start with, or in cases in which a rudimentary vagina has been created by the above mentioned technique, the outer edges of the pouch are separated from the vulva and undercut deeply (two inches). The whole pouch is then pushed inward and flaps are again cut from the edges of the vulva, and turned in to meet the edges of the counter-sunk pouch.

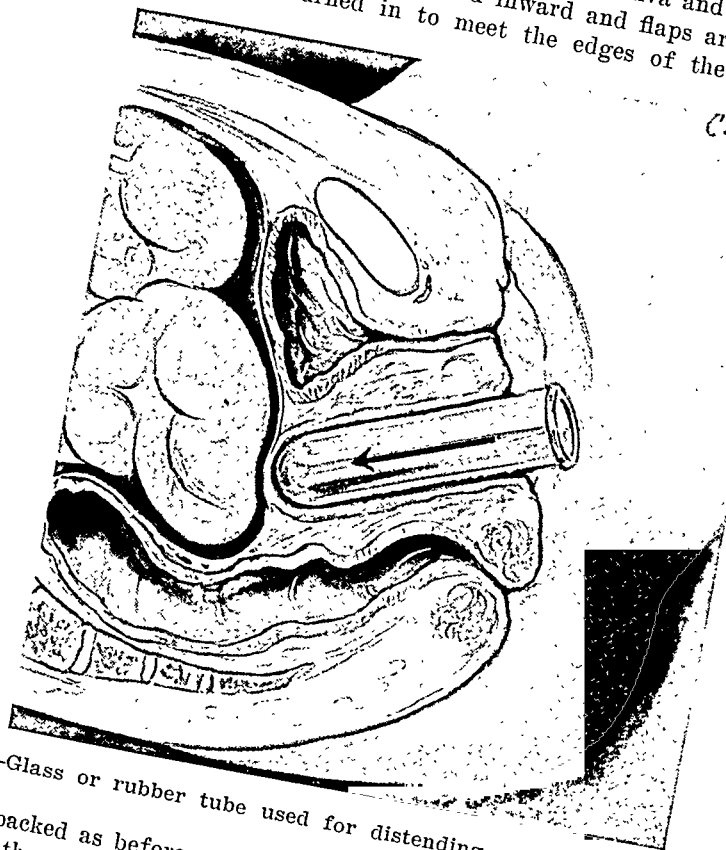


Fig. 6.—Glass or rubber tube used for distending and elongating pouch.

The cavity is packed as before. Epithelization again takes place between the flaps, and the pouch thus formed is five or six inches deep. Healing is usually complete in two weeks, after which further deepening of the pouch can be attained by daily stretching and by pushing inward with a vaginal plug. We have had no complaint of secondary contraction of the pouches nor of undue dryness of the epithelium. There is no hair growth on the strips turned in, so that there is no irritation on that score.

As in the case with most surgeons, my personal experience with the correction of this anomaly is limited to a few cases, some of which, however, have been sufficiently complicated to be of considerable interest.

CASE REPORTS

CASE 1.—In 1927, a 19-year-old white girl entered the Gynecological Service at the University of Iowa, complaining of cramplike pain in the lower abdomen recurring every month, but with no menstruation. She had had the symptoms off and on for two years. She was engaged to be married, had normal libido and had attempted intercourse on several occasions. On examination a pouch about one inch deep was found between the urethra and fourchette. Rectal examination revealed no mass or evidence of retained menstrual blood. I made a crucial incision in the vault of the rudimentary vaginal pouch and inserted a needle cautiously between

third layer of silk sutures which narrowed the urethra until it admitted a catheter snugly. The vaginal pouch was again deepened. The patient left the hospital having good control of the urine. Control was maintained for three weeks when the patient stated she passed something through the urethra (probably silk stitches) and following this incontinence returned. She returned to the hospital on Aug. 8, 1939, at which time the urethra was found to be much smaller but the patient complained of incontinence on standing. A urethral sphincter was made by crossing the bulbocavernosus muscles underneath the urethra from each side. This resulted in good control, and the patient had a perfect result when she left the hospital as far as the incontinence was concerned. The vaginal pouch, however, was still only about two inches deep, but it was thought best not to attempt further dilatation of this until complete urinary continence could be established for some time, for fear of weakening the newly formed sphincter, keeping in mind that the urinary incontinence was the principal complaint of this patient when she presented herself at the clinic.

CASE 8.—About two years ago a 3-year-old child was brought to our pediatric out-patient clinic by its mother. Examination revealed a total absence of the vagina. The mother was advised to do nothing about the condition, but to explain the situation to the child when it reached the age of puberty and to have her seek gynecologic advice should she later contemplate matrimony. Since in our experience these patients are usually mismanaged when seen by general practitioners and general surgeons, written instructions to the mother are advisable which should be transferred to the child at the proper age.

DISCUSSION

Since there have been so many successful operations proposed for the correction of this anomaly, one hesitates to suggest a different procedure. I was stimulated to develop the method here described by the impression gained from the literature that most of the methods had at least some minor objections. The technique was evolved with an eye to meeting these objections in whole or in part, and producing a safe operation that could be done successfully by men possessing the average skill in gynecologic surgery.

The method here proposed is totally devoid of danger. It uses to the utmost any rudimentary vaginal canal and vaginal epithelium that may be present. It gives a partially epithelized sac to start with, namely, the vault and the strips that are turned in. These form epithelization centers from which new epithelial cells grow out rapidly to cover the intervening raw spaces. There are no hair follicles on the skin that is used to form the pouch, and of course none on the areas covered by the epithelial cells that grow out from and unite the strips previously turned in. There is no irritating discharge from the tube and no unusual dryness of the canal has been noted or complained of by the patient. The turned in flaps and central disk have shown no tendency to slough, and the epithelization of the tube has been rapid and complete. This is probably due in a large part to the double blood supply to the flaps, the light pressure maintained by the gauze pack and the maintained blood supply of the central disk.

It is true that the secondary deepening of the tract in some cases necessitates a second hospitalization, but since the first step only requires about a week in the hospital, the total stay does not exceed that for many operative procedures. The operation may be done very well under local anesthesia.

remains of the round ligaments and the infundibulopelvic ligaments. The atrophic ovaries were left in situ. The results on leaving the hospital were good with the vault well suspended. On June 8, two months later, this patient returned with a complete prolapse of the vaginal pouch. I opened the abdomen in the midline, and freed a 5 cm. strip of rectus fascia 1 cm. wide from the lower angle of the wound on each side, leaving it attached at its pubic end. The pouch which was previously carefully prepared as for a total hysterectomy and packed with anti-septic gauze was pushed upward by an assistant with an eight-inch forceps from below. The vault was opened and the fascial strips were sewed into the angles of the pouch. The abdomen was closed around the strips. When seen several months later, the vaginal pouch was well supported, and there was no interference with bladder function.

CASE 6.—C. McR., white, American, aged 17 years, entered the hospital Feb. 16, 1939, stating she felt well and was unaware of the condition until seven months ago. For two months prior to coming to the hospital she had vicarious nasal menstruation, the last occurring on three successive nights and being scant. When 13 years of age on one occasion she had hemorrhages into the skin and from the mouth, which lasted only one day.

Examination revealed poorly developed breasts and scant pubic hair, normal external genitalia with a rudimentary vaginal pouch which admitted the tip of the fifth finger to a depth of 2 cm. Rectal examination revealed no uterus or right ovary, but a mass which was taken to be the left ovary in the left adnexal region. She was operated upon according to our technique with production of a four-inch pouch which contracted to three inches three months later. This illustrates the desirability of waiting until just before marriage in these cases before operating.

CASE 7.—M. V., white, American, aged 27 years, entered the hospital Feb. 13, 1939. At the age of 19 she was examined by a physician in Springfield, Illinois, because of a nervous breakdown, who told her she would have to have a "skin graft operation below" and referred her to a physician in St. Louis. Because of so much pain during the examination, she had to be anesthetized. On waking up she found that she could not retain her urine and has been incontinent ever since. At the age of 24 she became engaged to be married and had intercourse on several occasions. When 26 she consulted a physician regarding her incontinence and was for the first time told that she did not have a vagina. A combined abdominal and vaginal operation was done to cure the incontinence which resulted in failure before she left the hospital.

Examination revealed good general development; the breasts were small and poorly developed; the clitoris was hypertrophied and what appeared to be a normal vaginal orifice admitted two fingers easily. On inserting two fingers into this opening, however, there was a gush of urine, and it was evident that the pouch represented the dilated urethra. A medium-sized vaginal speculum could be readily passed, and on spreading the blades the interior of the bladder could be easily visualized. There was no evidence of a vaginal orifice, and no uterus could be palpated. Two masses in the adnexal regions were taken to be ovaries.

In this case two conditions presented themselves: It was necessary to perform an operation for incontinence caused by the tremendously dilated urethra and at the same time produce an artificial vagina. According to our technique of stretching the vaginal pouch after turning in the flaps, there was danger that any repair that might be made in the region of the vesical neck might be damaged by stretching. It was therefore thought advisable to attempt to produce the artificial vagina first and follow this by a plastic on the urethra. On February 22, and March 17, 1939, the first and second stages of our operation for an artificial vagina were performed. Following the second operation, there was moderate vaginal bleeding which necessitated repacking. On leaving the hospital, the vaginal pouch was about two inches deep. She returned April 18, 1939, for operation for incontinence. The vaginal pouch had contracted and was only about an inch and a half deep. The anterior wall of the pouch was incised and the dilated urethra and base of the bladder were plicated by two layers of No. 2 chromic catgut and the

In three or four of the cases in which this method was used at the clinic complete traumatic destruction of the vagina has been present. The vaginal canal of one of these patients was reconstructed by Dr. Counseller and the uterus later was connected with it: this woman has been pregnant and about three weeks ago a cesarean section was performed on her by Dr. Counseller.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—Being somewhat interested in mechanical devices, I felt I could improve upon the obturators used in these cases and built one in my own shop out of the modern plastics. I discovered that the plastic was a very undesirable thing to use, because the entire graft sloughed and the patient came near to developing a fistula. The plastic appeared to be corroded by the tissue. Since then we have used only glass.

The other point I wish to refer to is the administration of estrogenic substances. At present we are using large doses of estrogen which we hope will be of benefit in establishing the mucosa in these cases.

DR. EMIL NOVAK, Baltimore, Md.—In the early days I tried various sorts of plastic operations, using flaps from the vulva or thigh, and the results were disappointing, chiefly because of the tendency to contraction and shrinkage of the canal. My experience with the Baldwin operation has been far more satisfactory, and I still think that no other operation can give such a perfect imitation of the normal vaginal canal. On the other hand, it is very definitely a major operation, although my impression, based on the four cases in which I have carried it out, is that it should not be a difficult operation for anyone accustomed to doing abdominal surgery. The fact remains, however, that in these days of simpler procedures most of us will hesitate about employing the Baldwin operation because it carries with it the inevitable operative risk of any such major operation.

There is one precaution which I should like to stress, when operations for absence of the vagina are contemplated. One should make sure that the vagina is really absent, as I have seen several cases in which the perineal body was entirely solid behind what appeared to be the urethral meatus, but in which a vaginal canal was present, opening into the urethra a short distance above the meatus. This is not an infrequent finding in pseudohermaphroditism, and the practical point in such cases is to make certain that a cystoscopic or endoscopic examination is done. The recognition of this condition is of great importance to the patient, because the surgical problem is a far simpler one than the construction of an artificial vagina. All that is necessary in cases of this type is to open the perineal body, dissect loose the posterior vaginal mucous membrane, and suture it to the perineal skin.

DR. BENJAMIN P. WATSON, New York, N. Y.—No mention has been made yet of a bloodless method of making an artificial vagina. I have under treatment at present a case in which this is being attempted. This patient first came to me about six years ago when she was 14 years of age because of severe abdominal pain recurring and ultimately becoming continuous. Believing her to have an imperforate vagina her physician had made an incision in the perineum and found retained blood.

On examination a definite swelling was found on one side of the pelvis with no vagina or vulvar orifice. It was evident that she had a rudimentary uterus, and on opening the abdomen this was found to be the case. The usual band going across the middle of the pelvis was present, at one side a swelling about the size of a pigeon's egg; and on the other side a rudimentary horn. The tubes and ovaries were normal on both sides. The rudimentary horns were each removed.

The patient being now 20 and contemplating marriage, she came for consultation with regard to the construction of the vagina. From the previous incision made between the urethra and rectum in an attempt to reach the retained menstrual fluid, there remained a shallow depression. The treatment consisted simply of supplying the patient with a glass vaginal dilator and instructing her to push this into the depression in the vulvar region, attach a T-bandage to it and wear this over night. We have gradually increased the size of the dilators and today, two months

The results in these cases have been on the whole very satisfactory. There have been no general reactions or wound infections.

It is to be hoped that, for a time at least, gynecologists attempting repair in these conditions will report their findings and results, to the end that pooled experience may lead us to the most practical solution of this very interesting problem.

REFERENCES

- (1) *Dannreuther, W. T.*: AM. J. OBST. & GYNEC. 35: 452, 1938. (2) *Koff, A. K.*: Curtis' Obstetrics and Gynecology, Philadelphia, 1933, W. B. Saunders Co., 1: p. 577. (3) *Dupuytren*: Quoted by Judin, Surg. Gynec. Obst. 44: 530, 1927. (4) *Mackenrodt*: Zentralbl. f. Gynäk. 35: 1017, 1911. (5) *Baldwin, J. F.*: Am. J. Obst. 56: 636, 1907. (6) *Schubert, F.*: Zentralbl. f. Gynäk. 35: 1017, 1911. (7) *Frank, R. T., and Geist, S. H.*: AM. J. OBST. & GYNEC. 14: 712, 1927. (8) *Graves, W. P.*: Gynecology, ed. 1, Philadelphia, 1916, W. B. Saunders Co., p. 667. (9) *Wharton, L. R.*: Ann. Surg. 107: 842, 1938. (10) *Masson, J. C.*: AM. J. OBST. & GYNEC. 24: 583, 1932. (11) *Judin, S.*: Surg. Gynec. Obst. 44: 530, 1927. (12) *Rabinovitch*: Quoted by Judin, Surg. Gynec. Obst. 44: 530, 1927. (13) *Novak, Emil*: Personal communication. (14) *Meigs, J. V.*: AM. J. OBST. & GYNEC. 35: 465, 1938. (15) *Counsellor, V. S.*: Ibid. 35: 467, 1938. (16) *Babcock, W. G.*: Ibid. 35: 468, 1938.

30 NORTH MICHIGAN AVENUE

DISCUSSION

DR. JAMES C. MASSON, Rochester, Minn.—Dr. Falls' method of making an artificial vagina appeals to me as being simple and satisfactory but, as with all plastic procedures, it requires extreme patience and care in carrying out details, not only on the part of the surgeon but also on the part of the patient.

Until recently I have been an advocate of the Baldwin procedure. I felt that there was comparatively little risk to the operation and that the results were universally good. In my first ten cases the results were excellent and convalescences were absolutely normal for abdominal operations. Since then, I have performed the operation in four cases with two deaths, and I have now decided that the operation cannot be done safely in all cases. Both patients died from peritonitis as the result of sloughing of the isolated loop of ileum, owing to traction from a too-shortened mesentery. When the mesentery of the terminal portion of the ileum is long enough, the Baldwin operation is a comparatively easy procedure for any surgeon accustomed to intestinal work.

The advantages of the Baldwin operation are: (1) One operation, (2) short hospitalization, (3) no tendency toward contracture, and (4) a normal moist mucous surface. If the terminal portion of the ileum is used, there is no irritation of the skin from the discharge. There should be no danger of obstruction, either early or late, or of adhesions as the result of the anastomosis. The disadvantages are: (1) Unsuitable in some cases, (2) the risk connected with the operation, and (3) the undue amount of secretion. If not more than 10 inches (25.4 cm.) of ileum is used, the secretion is not a cause for worry or inconvenience to the patient and tends to decrease in amount.

Since 1936, at the Clinic we have used in 30 cases the McIndoe method or a modification of it, inlaying Thiersch grafts, and I am satisfied that this is a satisfactory and safe method. I think there are just three requisites to obtaining a good result by this method: (1) Meticulous care in obtaining a dry field to be grafted; (2) obtaining a one-piece, uniformly good thin skin graft; (3) use of an obturator for several weeks or until marriage. The results obtained by this method are so satisfactory that I doubt the advisability of performing the Baldwin operation except in special cases.

Perfect results are obtained with the McIndoe operation in about 50 per cent of cases. By a perfect result, I mean a complete take of the primary graft. In some cases secondary skin grafts or time for skin to grow over the total surface from isolated islands of skin and the long use of the obturator are required.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Sterility

Stein, Irving F.: Further Studies in Infertility and Sterility, Surg. Gynec. Obst. 67: 731, 1938.

An analysis of 200 childless couples examined in private practice showed that infertility was more frequently encountered than sterility. The male partner was responsible for about one-third of reproductive failures. Roentgenographic methods were of material value in investigation of the female partner. Pregnancy occurred in almost half of the matings in the infertility group and in only 15.4 per cent in the sterility group after investigation and treatment. Successful treatment in the infertility group was chiefly attributable to cervical cauterization, patency tests, and sex adjustments. In the sterility group, hormone therapy in the male and surgical treatment in the female were at times successful.

WM. C. HENSKE

Daniel, C., Mavrodim, D., and Waneff, A.: Research on the Permeability of the Tubes in Adnexal Inflammation, Gynécologie 37: 15, 1938.

The investigations of the authors lead them to maintain that the tubes are patent in cases of adnexal inflammation more frequently than is generally believed. In their cases they found the tubes open in 43.2 per cent. One tube was permeable in 24.3 per cent; whereas both tubes were open in 13.5 per cent. Tubal insufflation succeeded in opening the tubes in 5.4 per cent of instances of adnexitis. In two cases of post-partum and postabortal pelvic cellulitis, the tubes were patent, indicating that inflammation of the cellular tissue leaves the tubes intact and does not predispose to sterility. The authors maintain that tubal insufflation in cases of adnexal infections, when carried out correctly and prudently, is a harmless procedure even when the infection is acute or subacute.

J. P. GREENHILL

Palmer, Pulsford, and Christeas: Hysterosalpingography With Fluid Lipiodol, Bull. Soc. d'obst. et de gynéc. 27: 127, 1938.

One of the properties of ordinary lipiodol is its viscosity which has certain advantages and some disadvantages. The authors recently substituted fluid lipiodol, and they report their experiences with this type of lipiodol in 43 cases. They found the fluid lipiodol to be satisfactory in every way. In fact the x-ray pictures more truly represented the conditions looked for. The fluid lipiodol is well tolerated by the tissues and is more quickly absorbed than ordinary lipiodol.

J. P. GREENHILL

Held, E.: Occlusive Action of Lipiodol on Closed Fallopian Tubes. Contribution to the Study of the Origin of Foreign Body Tubercles in the Tube, Rev. franç. de gynéc. et d'obst. 34: 489, 1939.

It is not the purpose of this communication to report on the inflammatory complications which occur after hysterosalpingography because every one knows of these. Held limits his remarks to the disturbances brought about within the

after the initial treatment, she has a vagina into which a dilator can be introduced without pain for $3\frac{1}{2}$ inches. I feel that with continuation of this treatment and marriage very soon, this patient probably will have a functioning vagina.

DR. LUDWIG A. EMGE, San Francisco, Calif.—The technique described by Dr. Falls is very ingenious, but it makes no provision for a desirable depth of the artificial vaginal canal. My experience with various methods has taught me that it is absolutely essential to eliminate the connective tissue ridge which traverses the pelvis at a right angle in the region of the uterine "anlage." This ridge has to be severed by sharp dissection and the rudimentary uterine vessels ligated.

Ordinarily this is not done except possibly with the Baldwin technique. Failure to do this usually results in a vagina of about two and one-half inches which is not an adequate length under certain circumstances. It is for this same reason, I believe, that Frank's invagination method only produces short vaginas.

Recently I have adopted the Wharton technique and of the 4 patients operated upon 3 had a vagina of from 4 to 6 inches in length, as demonstrated by these lateral views of x-ray studies. In the first case I failed to appreciate the importance of the uterine ridge and the result was a short canal. The Wharton technique is extremely simple, requires only two to three days of bed rest, and eliminates the necessity of skin transplantation. Epithelization can be hastened considerably by the nightly introduction of estrogenic suppositories. The vaginal canal usually develops a firm, normal-appearing mucosa in from two to three months. I allow my patients to wear a well-fitting balsa wood plug covered with a rubber membrane for about six weeks. No other treatment is necessary, and there is astonishingly little discomfort or vaginal discharge.

DR. JAMES R. MILLER, Hartford, Conn.—Estrogenic hormones, it should be borne in mind, have a reaction only upon tissues of Müllerian origin. Response to them can be expected in the method that Dr. Falls has utilized, but if vulvar skin is used one would not expect any effect.

DR. FALLS (closing).—As to the question of cooperation on the part of the patient in using the obturators, I have not had the difficulties that Dr. Masson has referred to. Particularly in the young married couples one finds it very easy to get cooperation.

The mortality in the Baldwin operation is, of course, the greatest deterrent. The irritating discharge following it has also been a source of complaint in the experience of nearly every man who has performed this operation.

Estrogen is apparently not necessary. The skin at the edge of the vagina supplies plenty of epithelium and while estrogen may hasten its growth, it is certainly not necessary.

The bloodless method demonstrates what can be done by simple pressure. I do agree that it is absolutely unnecessary to cut clear to the peritoneum in order to get a vagina that will be long enough for normal cohabitation. The danger of this bloodless method, however, may be a partial prolapse such as occurred in our case in which the vagina was formed from the pressure of normal intercourse.

(The Presidential Address of Dr. F. L. Adair will be included in the December issue.)

fact that the volume of seminal fluid is ordinarily sufficient to overcome any unfavorable acidity during the brief period of time when such might be a factor. Survival of the spermatozoa is fostered by the increased alkalinity of the cervix, uterus, and tubes, forming in consequence a physiochemical gradient in which the sperm is caused to travel in the direction of the most favorable environment. In the cervix, uterus, and tubes, the hydrogen ion concentration is usually in the neighborhood of 8.6.

One might expect that an increased alkalinity of the vagina would seriously interfere with the migration of spermatozoa by an alteration in the potential, aside from the fact that the inflammatory process behind the altered pH might in itself interfere with sperm migration. In the opinion of Williams, conception following alkaline douches is more likely to be due to the cleansing effect than to the contained alkali.

The degree of motility is tempered by metabolism of the sperm, which utilizes either a small amount of stored energy or energy derived from the surrounding medium. If kept at a temperature which is low enough to impede motility, the survival time is greatly increased. This is apparently due to the fact that spermatozoa contain a certain amount of stored energy which within a few hours is utilized if stimulated by heat, and which is conserved by cold. Spermatozoa will retain their motility longest if kept in a refrigerator at about 8° C., but at ordinary room temperature (about 20° C.) will often be alive and highly active after two or three days. Motility is but little affected within the first two to four hours at room temperature.

The following procedure is suggested as a convenient routine method of making motility examinations of *in vitro* specimens:

1. Obtain semen samples by ejaculation directly into wide-mouthed bottles, after which the bottle is tightly corked and kept at room temperature (15° to 20° C., or 60° to 70° F.).

2. Within two hours after ejaculation, examine for motility, noting the abundance of cells, the ratio of motile cells and the degree of motility. A note should also be made of the presence of any leucocytes. For this observation, a drop of semen is placed on a microscope slide, covered with a cover slip and examined at room temperature. If no motility is present or if motility is sluggish, the specimen is warmed to about 37° C. and re-examined. This will often induce or accelerate motility.

3. Re-examine at eight- to twelve-hour intervals until motility has ceased. In the normal cases, motility of some of the cells should endure for two or three days.

J. P. GREENHILL

Laffont and Bourgairel: Association Between the Biologic Action of the Cervical and Vaginal Secretions on Spermatozoa, *Bull. Soc. d'obst. et de gynéc.* 28: 337, 1939.

In 34 sterile couples, the authors tried to determine whether there was any connection between the cytobacteriologic aspect of the cervical and vaginal secretions and their action on spermatozoa. They found that parasitic and bacterial infections of the vagina and urine prevent the normal activity of spermatozoa in the genital tract in two-thirds of the cases. On the other hand, in one-third of the cases, bacteriology does not explain the harmful effect of the vaginal and cervical secretions on spermatozoa and hence the authors turn to biologic incompatibility as the explanation.

J. P. GREENHILL

Watson, M. C.: The Effect of Cervical Secretions on the Vitality of Spermatozoa, *Canad. M. A. J.* 40: 542, 1939.

The author believes that deficient cervical secretion, tenacious mucus plugs in the cervix, and mild inflammation of the cervix present conditions hostile to the invasion of healthy spermatozoa. In a small series of sterile patients in which

Fallopian tubes due to the presence of a foreign body which is injected. He reviews the literature and mentions a number of instances of such complications. He reports a case in which in a sterile woman, with closed tubes, hysterosalpingography was performed. One tube had to be removed after this procedure because an adnexal inflammatory mass developed. Microscopic examination revealed an old chronic salpingitis with tubercles of foreign bodies. Hence, the author agrees with Rubin who cautioned that circumspection be used in the injection of lipiodol in cases where the tubes are closed. In the opinion of the author the chief indication for hysterosalpingography is in cases where the tubes are closed and operation is contemplated. The author agrees with Dannreuther that tubal insufflation should be the test routinely performed in cases of sterility and that the use of iodized oil should be restricted for special cases. Insufflation by the Rubin kymograph method will greatly restrict the indications for the use of iodized oil injections.

J. P. GREENHILL

Walther, O.: The Question of Embolism During Hysterosalpingography With Lipiodol, Acta radiol. 20: 457, 1940.

On hysterosalpingographic inspection it is sometimes found that the contrast fluid employed has entered the veins of the uterus and the pelvis. From there, the lipiodol is carried with the blood stream, via the common iliac vein, to the inferior vena cava, and thus for a short time becomes roentgenologically visible as a broad band parallel to the spinal column. Later, the iodized oil sticks to the arteries and capillaries of the lung, where it rapidly splits up into its two principal components, oil and iodine. Most of the iodine becomes excreted in the course of the first six to eight days, chiefly through the kidneys. Occasionally, when considerable quantities of lipiodol are injected directly into the vascular system, they may give rise to severe complications, or even be fatal, unless the now well-known precautions are duly observed.

J. P. GREENHILL

Laffont, A., and Bourgarel, R.: Sterility and the pH of the Masculine and Feminine Secretions, Bull. Soc. d'obst. et de gynéc. 27: 221, 1938.

The authors investigated the pH of the semen, vaginal secretions and cervical secretions of sterile couples. All of the examinations were made during the intermenstrual interval. Among the 12 cases reported, there was one case in which the semen had a pH of 8.2. All the others were less than this. The pH of the vaginal secretion was fairly constant and ranged around 4.5. On the contrary the pH of the cervical secretion varied considerably and this variability fluctuated according to the pathologic condition which was present. The authors believed that to overcome sterility it is necessary to overcome the excess alkalinity of the cervical secretions and not its acidity as is commonly believed.

J. P. GREENHILL

Williams: The Relation of Sperm Motility to Fertilizing Ability, Urol. & Cutan. Rev. 43: 587, 1939.

Motility is not *prima facie* evidence of fecundity. Motility is a function of the appendage, and does not indicate with any degree of certainty the condition of the sperm head, and its ability to unite with the ovum. It is an essential function of the healthy sperm if it is to migrate in the female genital tract and cause impregnation, but it is likewise an inherent characteristic of most spermatozoa that are not fit for impregnation purposes.

Spermatozoa are very sensitive to changes in hydrogen ion concentration, motility being impaired by slight changes in either direction. Ordinarily the hydrogen ion concentration of semen is about 8.1 to 8.4. The vagina has a pH of about 3.6 to 4.5, which would be incompatible for spermatozoa were it not for the

to overcome the local abnormalities; but in severe cases, surgery must be employed. Among the surgical procedures used to overcome tubal obstruction, the author mentions (1) salpingolysis, liberation of the adherent tube, (2) salpingostomy, the formation of an artificial opening in the tube, (3) partial salpingectomy, (4) subtotal salpingectomy with tuboovarian fixation, and (5) tubal implantation where the proximal part of the tube is removed and the rest of the tube implanted into the uterine cavity. He recommends an operation called total linear salpingostomy whereby the tube is cut open for its entire length from the fimbriated to the cornual end. He reports one patient operated upon by this method with a subsequent pregnancy.

The advantages of this operation are the saving of the entire tube and the maintenance of its normal blood supply and innervation. The operation is also excellent treatment for salpingitis, especially of tuberculous salpingitis.

J. P. GREENHILL

Villard: Salpingostomies in the Treatment of Sterility, *Bull. Soc. d'obst. et de gynec.* 27: 285, 1938.

Among the cases of salpingostomy performed by him, two patients had miscarriages but one had three pregnancies. In all, five living children were delivered. The author points out that the cases in which pregnancy occurred after salpingostomy were those in which the etiology of tubal closure was a puerperal infection. He did not encounter a single successful result in the gonorrheal cases.

J. P. GREENHILL

Robecchi, E.: Radiology in Female Sterility, *Ginecologia* 6: 1, 1940.

The author discusses the diagnostic pneumoperitoneum and its combination techniques, colpography and hysterosalpingography. His findings in 500 cases of female sterility having salpingographic studies are presented. Nearly one-third in this series were revealed to have normal tubal patency; 40.7 per cent evidenced bilateral tubal occlusion; 8 per cent unilateral tubal nonpatency; and 4.4 per cent were found to have a functional tubal occlusion.

The author lists nine complications that may occur incidental to hysterosalpingography. There are the various reactions of the Fallopian tubes to the introduced pressure used during the technique, peritoneal reaction to the iodized oil, penetration of the iodized oil into the blood vessels and lymphatics about the tubes and uterus, actual perforation of the uterine wall, late pain, endometriosis, ovarian damage from the roentgen rays, iodism, and last the interruption of an early pregnancy.

In the latter part of the article the writer discusses radiology as therapy in the treatment of female sterility. The author notes that pregnancy followed hysterosalpingography 31 times, and of these 2 were ectopic pregnancies. In conclusion, Robecchi discusses roentgenotherapy of the ovaries, hypophysis, thymus, and thyroid glands.

CLAIR E. FOLSOME

Glober, L. J.: The Treatment of Sterility, *South. M. J.* 31: 981, 1938.

There is involuntary sterility in at least 15 per cent of marriages. A complete history of the couple and a thorough physical examination of the wife are essential preliminaries in a solution of the problem. The investigation is facilitated by a consideration of four factors:

(a) *Male Factor:* Includes a careful history, and a detailed examination of semen obtained after a period of continence of approximately a week's duration. Moench and Hotchkiss' standards for male fertility have minimal requirements of normal viscosity, a volume of at least 1 c.c., with a sperm count of at least 60,000,000 per c.c., with less than 18 to 20 per cent of abnormal sperm.

one or more of the above were the only demonstrable abnormalities 100,000 to 150,000 international units of estradiol benzoate were given intramuscularly forty-eight hours previous to postcoital examination. He reports a definite increase in the amount of secretion available for examination, with a very marked increase in the number of actively motile sperm which could be recovered. He suggests this effect as a mechanism by which estrogenic stimulation may prove effective in some cases of sterility.

CARL P. HUBER.

Moench, G. L.: The Relation of Certain Seminal Findings to Fertility, With Special Reference to Sperm Concentration and the Significance of Testicular Epithelial Cells in Semen, *Am. J. Surg.* 47: 586, 1940.

The number of sperms produced ordinarily is far in excess of that needed to fertilize the ovum. Very long, tapering and narrow sperm heads are of especially sinister import and their shortening is often the first sign of improvement. By evaluating the clinical data, the sperm morphology and the presence and number of the protoplasmic drops and seminiferous epithelial cells, it is frequently possible to distinguish between sexual fatigue, testicular hypoplasia, and acute and chronic testicular tubule degeneration.

J. THORNWELL WITHERSPOON

Eastman, Guttmacher and Stewart: Experimental Observations on "Sperm Immunity" in the Rat, *J. Contraception* 4: 147, 1939.

The "sperm immunity" theory is based on the idea that parenterally injected semen produces specific antibodies (spermattoxins) which are lethal to spermatozoa introduced into the female genital tract. Such immune bodies, chiefly precipitins, actually develop in the blood sera of rats, as established by reliable investigators. However, in regard to the second implication of this hypothesis, namely, temporary sterility, seemingly convincing evidence has been advanced both in favor and against this resulting effect.

Thorough reinvestigation of this latter problem by the authors leads them to the conclusion that in white rats a slowly progressive decrease in fertility begins at the age of 12½ months, probably accounting for the seeming success with sperm injections in some experiments.

When one compares, age by age, the fertility of injected animals with the controls, it appears that parenteral injection of live sperm reduces slightly the fertility of the recipients, but the reduction is neither of significant degree nor of practical importance.

HUGO EHRENFEST

Dickinson, Robert L.: An Ensemble for Ovulation, *J. Contraception* 3: 219, 1938.

Dickinson from an analysis of a huge amount of material concludes that there is a "safe" period during the week preceding menstruation which, without protection, is as safe from conception as is intercourse guarded by any method except two. These are the condom, consistently tested before use, and the skillfully fitted pessary-with-jelly, unfailingly used.

It is the week following the period and during the period itself, in which his maze of assembled notes casts grave doubt, if not actual denial, of safety or sterility.

J. P. GREENHILL

Chalier, A.: Total Linear Salpingostomy for the Treatment of Tubal Sterility, *Bull. Soc. d'obst. et de gynéc.* 27: 242, 1938.

In the opinion of Chalier tubal disturbances account for about one-half of the cases of sterility in women. In mild cases, conservative measures may be used

Item

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held in June, 1941.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, from May 28 to June 1, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A (Part II) examinations must be on file in the Secretary's Office not later than March 15, 1941.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board wishes to announce a modification of the case record ruling (effective January 1, 1942) as it appears in the September, 1940, issue of the Board booklet. This ruling should read: "It is preferable that the number of cases submitted should not be more than half (25) of the total number of fifty (50) cases required."

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

BACILLARY AND RICKETTSIAL INFECTIONS. By William H. Holmes, Professor of Medicine, Northwestern University Medical School, etc., Chicago. The Macmillan Company, New York, 1940.

SEX IN DEVELOPMENT. Edited by Carney Landis, Associate Professor of Psychology, Columbia University; Principal Research Psychologist, Psychiatric Institute and Hospital. 329 pages. Paul B. Hoeber, Inc., New York, 1940.

CIRUGIA DE LA CONSTIPACION. Par el Dr. Conrado Zuckermann, professor de patologia quirurgica de la facultad de medicina de Mexico. Con 32 grabados. Mexico, 1939.

THE ANATOMY OF THE FEMALE PELVIS. By F. A. Maguire, Honorary Lecturer in Anatomy; Honorary Gynaecological Surgeon, Royal Prince Alfred Hospital, and Prince Henry Hospital in Sidney. Third edition, 162 pages, illustrated. Angus and Robertson, Sydney, Australia, 1940.

EXPECTANT MOTHERHOOD. By Nicholson J. Eastman, Professor of Obstetrics, Johns Hopkins University, and Obstetrician-in-chief, Johns Hopkins Hospital. 176 pages, illustrated. Little, Brown and Company, Boston, 1940.

PHYSIOLOGY OF THE FETUS. By William Frederick Windle, Professor of Microscopic Anatomy, Northwestern University Medical School. 249 pages, illustrated. W. B. Saunders Company, Philadelphia, 1940.

RECENT ADVANCES IN SEX AND REPRODUCTIVE PHYSIOLOGY. By J. M. Robson, Lecturer in Pharmacology University of Edinburgh. With introduction by Professor F. A. E. Crew, Director of the Institute of Animal Genetics, Edinburgh. Second edition, 539 pages with 62 illustrations. Blackiston Company, Philadelphia, 1940.

ABDOMINAL OPERATIONS. By Rodney Maingot, Senior Surgeon to the South-End General Hospital, London, etc. In two volumes, 1385 pages with 298 illustrations. D. Appleton-Century Company, New York, 1940.

(b) *Constitutional Factors*: The so-called "index of fertility," which depends upon the strength of the germ plasm, may be lowered by the presence of an anemia, obesity, marked malnutrition with vitamin and mineral deficiency, sexual excesses, syphilis, tuberculosis, and worry. Appropriate corrective measures should be instituted.

(c) *Mechanical Factors*: These prevent the union of the male and female germ elements. Approximately one-third of sterile women have diseased cervixes. The ingredient of human sperm which causes lysis of a normal cervical plug is interfered with when pus is present. Failure of the cervix to dip into the seminal pool requires postural treatment during and after coitus. The indications for artificial insemination are: (1) Effluvium seminis; (2) rare cases of persistent endocervicitis; (3) failure of cervix to contact seminal pool; (4) rarely, when the specimen is fertile but deficient in amount. The procedure must be performed with aseptic precautions, and it is best done just before ovulation. Tubal patency should be tested by the Rubin test or salpingohysterography. Operative procedures on the tubes may occasionally be indicated, but these are not often attended with success.

(d) *Endocrine Factors*: In the less obvious endocrinopathies these factors may be somewhat difficult to determine. In addition to the quantitative biologic tests when they are available, basal metabolic rate, glucose tolerance tests, and endometrial biopsies frequently offer useful information. Endocrine treatment is not standardized, and a number of agents are employed. The author expresses preference for thyroid extract, claiming that it apparently improves germ plasm of both sexes. Mention is made of three patients in whom spermatoxins were believed to have been responsible for the sterility. In a hanging drop, a saline suspension of sperm and wife's serum caused agglutination.

ARNOLD GOLDBERGER

Berutti, Enrico: The Etiology and Basis of Effective Therapy in Human Sterility, Ginecologia 6: 99, 1940.

The first center for the sole study and treatment of sterility in Italy was established at the University of Torino. The author, in a footnote, states that the activities of this clinic were of particular interest to Il Duce.

The writer offers a long statistical paper on the 1,050 infertile and sterile patients seen at the Torino Sterility Center. Of this group, 742 were diagnosed as having primary sterility, 288 classified as secondary sterility and another 20 instances gave an uncertain history of preceding menorrhagia.

Hypoplastic uteri were found in 221 cases of the 742 instances of primary sterility. The 3 major pathologic situations presented by gynecologic examination in the primary sterility group were cervical erosions (9.43 per cent), cervicitis (7.28 per cent) and uterine retroversion (8.49 per cent). Eighty cases (10.78 per cent) of the primary sterility series gave a history of previous laparotomy.

In the 288 cases of secondary sterility, it was observed that in 127 instances the sterility followed a single abortion while in 83 other cases it followed the first pregnancy. The 3 major diagnoses in this second group were: metroadnexitis (14.21 per cent), hypotrophic uterus (11.8 per cent), and endometritis and metritis (10 per cent).

Tubal patency tests were performed in 400 individuals and in 31.5 per cent both tubes were patent; in 40.2 per cent both tubes were found occluded, while in only 8 per cent the tubal occlusion was limited to one tube. The remaining cases evidenced functional occlusion, reduced or doubtful tubal patency. In 25 cases (6.25 per cent) showing tubal changes, a pregnancy followed hysterosalpingography. Pregnancy occurred in 11.9 per cent of the total 400 cases, but this latter figure includes the 126 instances showing normal tubal patency.

The large series of cases investigated under such ideal conditions make the author's study a worth-while contribution to the problem of sterility.

CLAIR E. FOLSOME

It is recorded in the notebook of one of his students which I have in my possession that Young stated:

"They began pretty early for to see the advantages of having this branch taught here, about 1725 and in 1726 Mr. Joseph Gibson was appointed to be the city professor and the Town Council enacted: That no woman should be allowed to practice midwifery in or about Edinburgh unless she had undergone an examination by some of the College Physicians and some of the Surgeons with the Professor of Midwifery and Mr. Gibson did intend to give lectures upon midwifery as he published a syllabus containing 22 lectures, but he never taught it as he died soon after, and as the midwives had not an opportunity of being instructed in this branch it was impossible for them to undergo any such examination, so that I have the pleasure of being the first who introduced the teaching of midwifery into this city, and though I met with many difficulties in getting the women to submit to be delivered by men, I have now got these difficulties pretty well over and we have now all the advantages in teaching it here that they have in any other places."

It will be of considerable interest to view the origin of the professorship of midwifery at Edinburgh. Some confusion has apparently arisen relative to this professorship because of difficulty in understanding the exact relationship between the authorities of the city of Edinburgh and the University of Edinburgh itself. Grant, in his story of the University of Edinburgh published in 1884, gives information relative to the establishment of a professorship of midwifery. This occurred on the ninth of February, 1726, when the Town Council added four new professors to the staff of the college and appointed a professor of midwifery. There was a distinction between this professorship and the other four in that the professor of midwifery was not professor at the college but was a City Professor. This was probably due to the fact that the college was for male students of medicine, and obstetrics was almost exclusively in the hands of the midwives. It was, therefore, not deemed necessary to teach medical students the art and science of obstetrics.

It appears that Mr. Joseph Gibson, somewhat ahead of his time, had practiced obstetrics in the town of Leith. Upon the insistence of members of the Colleges of Physicians and of Surgeons and largely upon his own initiative he was created by the Town Council the "Professor of Midwifery in this city and privileges to profess and teach the said art in as large an extent as it is taught in any city or place where this profession is already instituted." It appears, at least from a statement of Thomas Young in his notes, that Gibson did plan to teach obstetrics and prepared a syllabus for this purpose, but he never actually taught midwifery. Gibson died in 1739, and he was succeeded by Mr. Robert Smith who "received the title of Professor of Midwifery in this city's college with the same privileges and immunities which the other professors in said college do enjoy or that are known to appertain to a professor of midwifery in any other well regulated city or place."

Apparently neither Gibson nor Smith taught medical students in this branch. Gibson may have taught the midwives, but according to Young's statement he did no teaching because of his death before the plan was put into operation. It is of interest to note that the Council at Edinburgh seemed to be thoroughly unaware that they were creating a precedent. The first professorship on the continent was at Strasbourg and was founded in 1728. Obstetrics was taught in other places both in

American Journal of Obstetrics and Gynecology

VOL. 40

DECEMBER, 1940

No. 6

Original Communications

PRESIDENTIAL ADDRESS*

AMERICAN GYNECOLOGICAL SOCIETY

FRED L. ADAIR, M.D., CHICAGO, ILL.

THE theme of my address is perhaps unusual. Man the Unknown, might be a suitable title but it savors of plagiarism so I will call it, A Man, Little Known. Him to whom I refer must have had considerable influence upon modern obstetric education and practice. He was a product of the Edinburgh University or of the educational atmosphere of the Edinburgh of the eighteenth century. He left no published books, though some notebooks, apparently those of students, written in longhand are extant—how many there are I do not know, but I have seen three. The name of him to whom I refer is Dr. Thomas Young, first lecturer and full Professor of Midwifery at the University of Edinburgh.

Turner in his history of the University of Edinburgh states that

“It is a noteworthy fact that in the year 1726, when John Rutherford and Andrew St. Clair began assiduously to teach medicine, the Town Council made, in the person of Joseph Gibson, the first appointment of a Professor of Midwifery in Britain. He was succeeded by Robert Smith in 1739, Thomas Young in 1756, Alexander Hamilton in 1780, James Hamilton in 1800, and Sir James Young Simpson in 1840. It is remarkable that the class of Midwifery did not become compulsory for students until 1833, after great exertion and legal action by James Hamilton, the Professor.

“The Maternity Hospital of the present day had its origin in the attic storey of the old Royal Infirmary which, under Professor Thomas Young, early in the eighteenth century, had been devoted by the Managers of this Institution to the treatment of lying-in women. Here practical instruction in obstetrics was given by Young and by Alexander Hamilton who, towards the close of that century, took over Park House, on the site of the present University Union, as a private hospital for this purpose.”

*Presented at the Sixty-fifth Annual Meeting of the American Gynecological Society, Seignior Club, Que., June 17 to 19, 1940.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their “Original Communications.”

name appears in the records of the Royal College of Physicians of Edinburgh as having received his Diploma Nov. 3, 1761, at Edinburgh, which was followed by a license to practice Dec. 8, 1761, and of his admission to Fellowship on Nov. 2, 1762.

He published in Rotterdam a thesis under the date of 1769, in Latin, the abbreviated title of which is "De Lacte," in which he is cited as a Briton graduated in Edinburgh Nov. 30, 1761.

Professor Simpson, in his historical article states that, "he had in his possession three manuscript notes of Young's lectures which were sometimes in one and sometimes in two or three volumes." He states that "they bear evidence to his wide acquaintance with the literature of his subject, and his excellent power of observation and exposition."

Professor Hamilton, adjunct and successor of Professor Young, wrote the following statement of him:

"This, among many other happy consequences, has been the effect of the public instruction of midwives, a measure introduced into Scotland by the late Dr. Young. Before this time any woman of intrepidity and address who chose to practice midwifery found employment; and for a while it required all his industry and professional talents to show the folly of trusting the delivery of women to such persons. Even they who pretended to the sacred name of philosophers joined in the prejudice. Dame Nature, they said, is the proper midwife, and nobody can be better qualified to attend to her dictates than Dame Ignorance. Dr. Young might with great facility, by publishing a few of the horrible blunders committed by the midwives resident in Edinburgh when he began practice, recorded in his note book (which is still in existence), have offered many most powerful arguments against such opinions, but he preferred the more philanthropic and dignified method of showing by its effects the utility of his plan. Such has been the public conviction on this subject that in the present day there is scarcely a parish of Scotland the midwife of which has not been regularly taught. If the difficulty of instructing women to act as midwives, and Dr. Young's disinterestedness in that task were universally known, a just tribute might be paid to his memory."

The following are some of the official records which evidence Young's pioneer work in the teaching of midwifery. He apparently established free home delivery service as he made public announcement of the fact that patients would be delivered in their own house free of expense. It is also a matter of record in the history of the Royal Infirmary that "in 1756 a ward in the attic story of the hospital, by the permission of the managers, but at Dr. Young's expense, was fitted up for four lying-in women, or as many more as Dr. Young could accommodate, each exceeding the number four paying sixpence per day to the house."

Dr. Young alone taught his classes for 24 years, and in 1780 he and Dr. Alexander Hamilton were made conjunct professors of midwifery. This arrangement enabled Dr. Young and Dr. Hamilton to give courses of instruction alternately, three in number, each year to male and female pupils. On the death of Dr. Young, Dr. Hamilton continued as the sole professor of midwifery, in 1783.

Largely through the efforts of Professor Hamilton and the activities of the Earl of Levan and Melville, the Edinburgh Lying-in Hospital was established in 1791. Certain rules of the Royal College of Physicians at Edinburgh promulgated at this time are of interest in this connection and show the attitude toward midwifery and the shifting opinions which occurred in the space of a generation.

England and on the continent. Literature emanated from men interested in midwifery in various cities and countries, but little, if any, had come from Edinburgh at this early date. It is difficult in this day and age to comprehend the many obstacles which were thrown in the way of so-called men midwives. There was a very great prejudice against men even being present at the time of birth. It, therefore, took a great deal of courage and foresight for the Colleges of Physicians and of Surgeons, for the Town Council, and for Mr. Thomas Gibson to advocate the practice of midwifery by men and to create a professor in the city of Edinburgh who would be responsible not only for the training of the midwives, who were at that time receiving no education in midwifery in that area, but also to envisage the future training of medical students as men midwives. The profession was considered unbecoming for gentlemen and improper or immodest for the women being delivered.

Professor A. R. Simpson has written an extensive article relative to the history of the chair of midwifery at Edinburgh. This lecture was published in 1882.

He says, "It would have been interesting to have known more than we do of Mr. Joseph Gibson, who was probably the prime leader in the whole transaction, and who was certainly the first Professor of Midwifery in the United Kingdom, if he was not indeed the first to fill an obstetric chair in any University." There is a paucity of information relative to this man who is described as "surgeon at Leith, member of the Society of Chirurgeon-Apothecaries in Edinburgh, and city professor of midwifery."

As City Professor Mr. Gibson, having the right to teach, still was not a member of the medical faculty of the University and had no place in the *Senatus Academicus*. Very little is known of Gibson and his activities. He died in 1739 after serving as City Professor for 13 years.

Mr. Robert Smith succeeded Mr. Gibson and we have the following notes from Dalzel's *History of Edinburgh University* which he has quoted from the proceedings of the Town Council:

"On February 9, 1726, Mr. Joseph Gibson, upon petition, appointed City Professor of Midwifery, but without fee or salary." Also the entry of Dec. 14, 1739: "Mr. Robert Smith, surgeon, elected Professor of Midwifery in the College, on the death of Joseph Gibson, Professor thereof in the city, but without a salary." (Smith's commission was ampler than that of his predecessor; it constituted him a member of the Senate. He held this Professorship 17 years.)

What he did and what he wrote is a mystery. He was a member of the *Senatus* and yet was never admitted as a member of the medical faculty. There is no available record of any of his activities or publications. On Feb. 18, 1756, the following note appears in the proceedings of the Town Council: "Mr. Robert Smith's demission of the Professorship of Midwifery in the college of Edinburgh. Thomas Young, surgeon, chosen in his place. No salary." (Young opened a class for students in this branch of medical practice, not confining his attention to the education of females.)

Dr. Thomas Young apparently had been teaching midwifery in Edinburgh since 1750 and was evidently a very energetic individual, but no record of his activities, of his birth, education, etc., is available. His

He clearly states that Smellie was the first who made any considerable improvement in teaching midwifery.

It is curious that while Gibson is mentioned, the name of Smith does not appear in the manuscript which I possess. It is interesting to note that Young records an interesting item that "Chapman was the first to discover the secret of forceps and reported six cases which he delivered with them." He makes this comment relative to Mr. Chapman: "Whereas before that time they (forceps) were only known to the Chamberlains so that the material contained in these books (Chapman's) is the discovery of the forceps. He likewise pretended to a secret pellet (for it was the fashion of the time that every practitioner be possessed of some nostrum either of the pellet or of some quickening pill or powder which assisted the labour more quickly) but his secret pellet died with him."

Young devoted considerable discussion to the theories or system of generation. He makes the following comment: "But it is evident that we are still much in the dark in regard to this matter. After all the theories that have been started we can't see why there is not a regular communication between the ovaria and the fallopian tube. It seems, however to take place at some time. Nor is it easy to explain how the male liquor enters the uterus and so in short every system that has been offered upon this subject is liable to the greatest objection, and we will not be able to understand it thoroughly."

He discusses ectopic pregnancies and states that they seldom come to any degree of perfection, seldom larger than three or four months and that they are more common in the ovary than in the tube.

He devotes considerable discussion to the toxemias of pregnancy, recognizing those cases associated with marked edema or dropsy and also the cases associated with fits or convulsions. These latter he divides into two main groups, those women who gave a history of having had fits, probably epileptic seizures, and those without such an antecedent history. The latter he regards as much more serious.

A few of his comments relative to these cases may be of interest. With reference to the fits he says:

"These will happen to women with child that never had the disease before; and they happen more frequently in a woman's first child than afterwards perhaps owing to this that the irritation is greater from the nerves being more sensible than they are ever afterwards. If the woman has been subject to these fits before there is less danger to be apprehended from them. These are also more or less dangerous in proportion to the frequency and when they are very frequent the woman frequently dies."

He reports a case upon which an autopsy was performed and no cause of death could be determined. The etiology is explained in the following paragraph:

"The fits may be owing to a great many different causes. The common cause is from the uterus pressing upon the iliac arteries. When this pressure is very strong it affects the aorta and by preventing the same quantity of blood from going to the under parts it occasions an overdilatation of the vessels of the brain, and the woman being at this time in a plethoric state the circulation is rendered more languid which may favour the production of these fits."

"17th May 1765.—An act was passed declaring that for the future no person should be admitted to be one of the Fellows, 'whose common business it is either to practise Surgery in general, or Midwifery, Lithotomy, Inoculation, or any other branch of it in particular; and further, that if any member of the College shall, after his being received a Fellow, practise any of these lower acts in the manner above mentioned, and shall thereof be lawfully convicted, he shall be degraded from the honour conferred upon him when he was admitted a Fellow, and his name shall be struck out of the Roll.'

"7th February 1769.—After full consideration by a Committee, and repeated discussion in the College, an Act was passed providing that no Fellow or Licentiate of the College should exercise the business or profession of Midwifery, Lithotomy, or any of the other manual operations of Surgery; and providing that, if lawfully convicted, he should be fined 40 pounds Scots for the first offence, and for the second, if convicted, he should forfeit his right of Fellowship, if a Fellow of the College, or his right of Licence, if a Licentiate, and all right and title whatever to practise physic within the city of Edinburgh and liberties thereof.

"7th November 1769.—The Act of 7th February was rescinded.

"6th August 1772.—The Act of 17th May 1765 was amended on the Report of a Committee to whom it had been remitted for consideration."

I have had little opportunity to peruse the manuscript notes of Young's lectures which are in the Library of the Surgeon General at Washington. However, one of them is an exceptionally beautiful example of manuscript notes. The title page bears the name of John Whyte and is dated the 14th of November 1771. This John Whyte subsequently became Whyte-Melville through marriage and is undoubtedly the Earl referred to as being influential in establishing the Edinburgh Lying-in Hospital. This manuscript is beautifully executed. The title page bears a quotation, Genesis, Chapter 3, Verse 16, "In sorrow shalt thou bring forth children." The first paragraph on page one is similar to the initial statement in the manuscript copy which I possess. I quote from the manuscript copy of John Whyte: "The word midwifery is taken in two different senses, the one is limited and confined and the other more extensive. The first takes in only the delivering of pregnant women, the second not only includes the operation but also all the diseases incident to unimpregnated women as well as those in pregnancy and after delivery."

The other notebook in the Surgeon General's Library is undated, but is beautifully written and prepared. The first page reads as follows:

"As Midwifery is a modern operation, consequently its history is shorter than that of the other Branches of Physic. I shall now go on to mention some of the measures that have retarded that Branch and then the several steps that have been taken to cultivate it. Long and sad experience have taught us in the clearest manner that this is one of the most useful, if not the usefulest operation in Surgery. For by it you often save two lives as in praeternatural cases and violent floodings when danger to one or both is very often unavoidable. Whereas by the help of a skillful operator we will often be able to save both from their impending danger. It lay a long time uncultivated from its being entirely in the hands of women and these the most illiterate, having no education and no skill of the anatomy of the parts. In fine all the learning they had was from Experience: hence we need not wonder at the blundering on from century to century. The Athenians were so sensible of this that they made a law against any woman practising Midwifery. In consequence of which a woman dressed herself in men's clothes, went away and was educated, came home again and practised midwifery and got into all the women's secrets. However she was detected and forbid to practise any more."

more important that you do not carry the incision too high or too low as the bowels are in danger of coming out, therefore the best place to begin is just a little above the navel and it is of advantage never to go too high. Some pinch up the skin in order to make the incision, lest they should open any considerable branch in an artery in which case the blood is in danger of getting into the cavity of the abdomen. However, it is very easy matter to take them up. You cut cautiously till you once get admittance for your finger which you are then to use for a director for your scalpel. Having got into the cavity of the abdomen you know the uterus from the other parts from its firmness and its being of a different color, then as before you first make a small incision for your finger and using it as a directory for fear of injuring the child you proceed to lay open the uterus, but were you to go on gradually cutting here as in the other parts the large uterine vessels would not be allowed to contract but would continue to pour out their blood. You therefore cut the rest quickly and get out the child as soon as possible whereby the incision is diminished the one half and the size of the vessels are proportionately lessened. If the child's head is much locked in the pelvis you will find a difficulty in getting it out. In this case you cause some one to introduce a hand into the vagina and push up the head while you pull the body. Also in consequence of this sudden contraction of the uterus the placenta is readily disengaged and you get it away with great ease. You next clear away all the extravasated blood that is upon the intestines, etc., and you bring the lips of the wounded uterus as close together as you can after waiting a little until the blood is pretty much stopped. You next bring the external parts of the wound together by the quill suture. You need not make the ligature so close below as the bowels are chiefly in danger of coming out at the upper side, and a small opening at the lower part of the wound serves for the passage of any moisture that may be generated. It is not necessary to take up the peritoneum and you tie the ligatures with a loop in case you find it necessary to untie again. The most disagreeable and hardest to be remedied accident that attends this operation is the forcing out of the intestines, as the handling them in order to reduce them often excites coughing, vomiting, etc., with protrusion anew."

He had performed the operation twice at the time of the unknown date of my manuscript copy, with the loss of two mothers and one baby.

He understood the mechanics of labor well and gives a clear description of the indications for operative and delivery technique. He discusses the management of the third stage and gives the following lucid instructions:

"The uterus is so formed that the moment it is freed of its contents it only contracts by degrees so that everything which is in it comes to be expelled but to forward this extraction you twist the umbilical cord around your hand and pull from side to side making the woman press down a little, and when it comes to the external os you move it in a circular direction. The proper time to begin is when the woman has afterpains which are proof that the uterus is beginning to contract. You are not, however, to expect that you will always succeed immediately. It may be ten to fifteen minutes and even an hour sometimes before you get it away, but you will generally succeed at last and with perfect ease to the woman."

He appears to have been greatly interested in the phenomenon of respiration and discusses the necessity of breathing air for both oviparous and viviparous animals. He quotes Harvey's opinion to the effect that the fetus may live some hours wrapped in its membranes without breathing. He quotes an experiment by Buffon "who confined a pregnant bitch so that she was under the necessity of dropping her young into a quantity of warm water which he placed to receive them; the animals remained several hours in this fluid and were quite lively and well."

He describes methods of resuscitation and emphasizes the necessity of removing anything from the face or mouth which might interfere with respiration and suggests the use of a female catheter to force air into the lungs and stimulate respiration.

He says: "There occurs also an irritable system peculiar to pregnant women." The outlook for the women who have these fits during labor is better than those who have them during pregnancy. He makes an interesting observation that the outlook is better for those who have had the fits before and also for the women who come out of them and recover their senses more quickly. He recognizes that the usual remedies for fits are of little or no service to pregnant women. He advocates venesection and prompt delivery as the best means of treatment.

It is curious that he gives the period of gestation as 270 to 275 days or 39 weeks. He also discusses premature births and makes a very interesting comment to the effect that "the child is often born in the seventh month and children were more commonly supposed to live then than when they were born in the eighth month because they thought the child made an effort to be delivered at the seventh month and if it did not come away then it required 40 days to recover strength, therefore if it happened to be delivered in the eighth month and being still fatigued it died, but this notion is not just, for the older the fetus the greater is the probability of its living."

Relative to the labor itself he says: "You need make no change in your dress for natural labour. Formerly as soon as a man midwife entered the room he put off his waist and put on his nightcap, put off his coat and put on a nightgown and put up his sleeves to his shoulders, but all this must cause a great terror to the woman, and in natural labour it is not necessary to make any change upon your dress. It is easy to slip up the sleeves of your coat and to take out the button of your shirt and put it up a little to keep it clean, and as you are generally situated behind the curtain you may do it unobserved, and those who wear a ring should take it off as it would injure the woman when the hand is introduced into the vagina."

He divides births into natural birth, laborious birth, and praeternatural births. He taught that "many things have been recommended in order to further the births but in many cases patience will do much more than any medicine. These at times have been thought successful because the delivering of a woman is a natural operation, so if your medicine is well timed it seems to do good and at other times it is rather too late and the woman is delivered before it arrives."

He thought forceps could be used for delivering women with the following positions of the head: "when the hind head is toward the os pubis, toward the os sacrum, when the face is toward one os ischium and the occiput toward the other."

He advocated the reduction of the following positions before the application of forceps: "when the chin is toward the os pubis, when it is toward one side of the pelvis, and when it is toward the os sacrum."

His indications for cesarean section are as follows: "It is performed when the mother is dead to save the child and also when the mother is alive in order to save both her and child, when from the extreme narrowness of the pelvis it is impossible to extract the child the other way. No one ever disputed the propriety of the operation in the former case; nay, in some cases it was considered as a capital crime to prevent the opening of the woman when dead in order to procure the child. In the latter it has not been so universally submitted to, and it is evidently as necessary here as in the other as without it a mother and child must both infallibly perish. While by means of it there is a possibility at least of saving the mother and a certainty almost of preserving the child."

He gives the following description of the operation:

"Before the operation it is proper to give the patient a quick dose of physic or an injection in order to empty the bowels. This done you either place her on a table or bed in such a manner that she may be half lying and half sitting as when one is cut for the bubonocoele. The operation is generally performed upon the left side in order to shun the liver, but it is not material whether you do it on the right side or left side as the uterus rises above the liver and sometimes the uterus inclines more to one side than to the other, in which case the side to which it is most inclined should be preferred. You make a mark on the skin as far as you intend cutting, the length requisite is about 8 inches and the incision is generally made half way between the navel and spine of the ilium, but it is not very material, and it is

that you may use more freedom. After the delivery you should make yourselves tolerably decent before you go out of the room in order to give some time to the nurse to shift the patient; and when you have allowed time for this you may return to give your prescriptions. A degree of secrecy is very necessary. Therefore you should beware of relating the oddities of one patient to another, for if you do she will naturally think that you will do the same to another with regard to her. If your patient has a peculiar distemper and you can relate to her perhaps a similar case, it may be of service, but you must never act wantonly in these cases; and you must be still more cautious in revealing to any of her own sex what you learn; and therefore in every case you must act and speak with the utmost decency and decorum, and never betray the confidence reposed in you by harbouring any bad or indecent design. They are little acquainted with the greater and better part of the sex who expect that women will forgive such faults. Errors in judgement they may forgive, but such behavior they never will, whereas if you behave in a becoming manner there is no fear but success will attend you, which that it may is the sincere desire, of your most humble servant—Thomas Young.”

In concluding this necessarily brief record of Professor Young it should not escape our notice that men who subsequently became very influential in our own country received their education and were granted their degrees during the years when Professor Young was Professor of Midwifery in the University of Edinburgh. He was one of a galaxy of brilliant men associated with the university of that period. His fame is less than theirs, but nevertheless he must be credited with founding modern concepts and methods of teaching midwifery. It is important to emphasize that Edinburgh through its Town Council and university unwittingly and without ostentation created the first professorship and university department of midwifery (1726-1756), which is recorded in the world literature.

These concepts and methods were brought back to our country by such men as William Shippen of Philadelphia, Samuel Bard and John Tennent of New York. It is impossible to calculate the influence of a man who has left so little written record of himself or his works, and we can only surmise that he must have had a very potent influence in the community and in the world at large. I have already mentioned the manuscript in the Surgeon General's office bearing the signature of John Whyte who later became Whyte-Melville and undoubtedly became interested through his contact with Young in establishing the Lying-in Hospital at Edinburgh.

William Drennan, a famous Irish patriot and writer, studied medicine in Edinburgh and graduated in 1778. This Irish patriot, writer, and poet subsequently practiced medicine in Ireland. In some records written while he was a student in Edinburgh he refers to the first course in midwifery by T. Young and says that “after dinner I have seldom more than 1 hours attendance at the college and that is on midwifery.” He entered the University in 1773 and sat for his examination in 1778.

It was through an accident a number of years ago that I acquired this manuscript copy of Young's lectures in Edinburgh. It is undated, but probably was written in the latter part of 1771 or during 1772. It could not have been prior to 1770 or 1771 as he gives references to these dates in the manuscript.

It has been with a great deal of pleasure that I have endeavored to unearth and clarify some of the facts with reference to his life and his

He evidently carried on some experiments of his own and calls attention to the effect of closure of pores in the eggshell on the accumulation of air within the egg and the effect upon the development of the chick.

He advocates milk as the proper food of all viviparous animals and contends that no milk is so well adapted for children as mothers' milk. He argues against the use of purgatives for newborn infants in spite of the fact that he recognizes a general prejudice in their favor.

He has a paragraph or two relative to puerperal fever, and he did thoroughly cleanse the ward and take measures to remove the "pestilence" as he termed it and subsequently had only one case which died in the ward where he had removed the bedding and substituted fresh bedding and thoroughly washed the room with soap and water.

The following is a quotation which concludes his discussion of puerperal fever:

"In this way then we have found no particular cure for puerperal fever but cleanliness is perhaps the best thing in order to prevent it from taking place. Purgatives, emetics, camphor bark and all the different antiseptic medicines have all failed in removing this here disorder."

He gives some pertinent advice relative to the selection of a nurse: "You should choose a woman who has all the appearance of health, who has no disease either hereditary or acquired, as this is a matter of consequence. Care must be taken to examine her children to see whether they have any appearance of any disorder as the scrofula does not appear on children generally speaking before the third or fourth year; for satisfaction in this matter you may examine her parents or brothers and sisters."

He closes his series of lectures with some advice to his students:

"Before we part I shall give you some few directions with regard to your conduct. Some of you are going immediately to enter upon practice. I told you it was unnecessary to read any books in the first course, but now you must consult some of the best authors upon this subject as you will now be able to read them with pleasure and benefit. You should therefore consult the writings of LaMotte, Mauriceau and Smellie; and you can't have a better compendium than in the writings of van Swieten, who has wrote very fully upon the diseases of both Women and Children, as you must be as much master of cases as possible in order to be able to give a certain prognostic by which you will at least gain reputation, when you cannot cure; so you must not only take the assistance of these cases you read, but of those which happen to yourself; and I can assure you the one who writes down his cases will have more experience at the end of 5 years than another who does not will have at the 10 hundredth. You should therefore write down in a day book what has happened during the day, where you succeeded and where you failed; particularly in the laborious cases which will plague most, and you must mention the progress of the dilatation of the mouth of the womb and the whole progress in short of the labour.

"It is common to mention the necessary qualifications for a man midwife. They are pretty much the same with those of a good operator, only a greater degree of composure is here necessary; for a small oversight is of the greatest consequence; and in other operations you have the assistance of your eyes, but here you have no such assistance. A becoming share of modesty is especially necessary here. You should not put any question to your patient which will shock her, and you had better put them to another as to her maid, her nurse, etc., especially if they are such as can be fully answered by a third person. When you are called to assist women in natural labours you should not be in too great a hurry in putting them to the touch; it will be proper to put them to bed, to darken the room to a certain degree, and to have as few assistants as you can, and you should make as little alteration in your dress as possible. Everybody knows what should be done in a common labour so your conduct will be strictly observed and the smallest blunder will be severely censured. In a praeternatural one they do not know so well what is necessary so

HORMONAL STUDIES IN ARTIFICIAL MENOPAUSE PRODUCED BY ROENTGEN RAYS

IRA T. NATHANSON, M.D., CHARLOTTE RICE, A.B., AND
JOE VINCENT MEIGS, M.D., BOSTON, MASS.

*(From the Harvard Cancer Commission and the Laboratories and Endocrine Clinic
of the Collis P. Huntington Memorial Hospital of Harvard University)*

INTRODUCTION

SINCE 1930 it has been the routine in some of the cancer clinics of this community to inactivate ovarian function by means of the roentgen ray in patients who have carcinoma of the breast before the menopause. The rationale of this therapy is to avoid possible stimulation of malignant breast epithelium by the ovarian hormones.¹ Regression of osseous metastases has been noted following such treatment.² A group of patients so irradiated offer an excellent opportunity to study the hormonal changes attendant upon this type of menopause, especially since the patients had no demonstrable disease of the genital organs.

In this investigation studies of urinary excretion of the follicle-stimulating hormone (gonadotropic hormone, prolan A) and estrogenic substances were made at frequent intervals on the urine of 10 patients who were thus irradiated following radical mastectomy. Two other patients, one a surgical castrate and a second sterilized by radium, are included in the series for comparison. Random observations were made on 10 other patients who had been sterilized prior to this study. In most instances, assays of the urine for follicle-stimulating hormone and estrogens were made for a short period preceding irradiation of the ovaries and thereafter at regular intervals during periods varying from one and one-half to three years. The patients were examined and questioned carefully at each visit so that the first signs and symptoms relative to the menopause could be correlated with the laboratory findings. Symptoms of the menopause were considered to be cessation of menstruation with accompanying hot flushes, night sweats, dizziness, increased nervous tension, and atrophic changes in the vagina.

TECHNIQUE OF OVARIAN IRRADIATION

The following factors were used to effect ovarian sterilization: 200 K.V., $\frac{1}{2}$ mm. cu. filtration, distance, 50 cm. or 77.5 cm. Total dosage varied from 1,200 to 1,600 r. divided over a period of four days and given through anterior and posterior portals. The portals were 10 cm. by 10 cm. or 15 cm. by 15 cm. Various combinations of the above factors, maintaining a constant voltage and filtration, were used to determine if possible the most efficacious means of obtaining the desired result.*

METHODS OF HORMONE ASSAY

The original technique of Aschheim and Zondek for determination of the urinary follicle-stimulating hormone was employed. This consisted of an alcoholic precipi-

*We are indebted to Dr. Richard Dresser for carrying out the above procedures.

influence. He apparently worked thoughtfully, seriously, and energetically with enthusiasm over a period of at least 33 years, and he was the first full Professor of Midwifery, the first teacher of medical students in midwifery at the University of Edinburgh which post he filled for 27 years. Men well known receive adequate praise and credit as well as criticism at times for their accomplishments. The man little known doubtless received much satisfaction from his work and made no effort to secure the acclaim of others. Thomas Young undoubtedly deserves great credit and unsought praise for establishing a great work in obstetric practice and education. He founded in Edinburgh University the modern concept of the teaching of obstetrics, and his influence has continued there and has spread through his students who became pioneers in obstetric teaching in our country. We should acknowledge our debt to him by belated but sincere praise.

REFERENCES

- Comrie, J. D.*: The History of Scottish Medicine, pp. 300, 304, 453, 455, 629. London (Wellcome Historical Medical Museum), Balliere, Tindall, and Cox, 1932.
- Curtis, A. H.*: Obstetrics and Gynecology, Vol. I, Philadelphia, 1933, W. B. Saunders Co., pp. 108, 109.
- Dalzel, A.*: History of Edinburgh University, Vol. II, Edinburgh, 1862, pp. 395, 408, 426.
- Fasbender, H.*: Geschichte der Geburtshilfe, Jena, 1906, G. Fischer, p. 324.
- Glaister, J.*: Dr. William Smellie and His Contemporaries, Glasgow, 1894, James Maclehose and Sons, p. 282.
- Grant, A.*: The Story of the University of Edinburgh. Vol. I, London, 1884, Longmans, Green, and Company, p. 315.
- Historical Sketch and Laws of the Royal College of Physicians of Edinburgh, from its Institution to August, 1891. Edinburgh, Morrison and Gibb, 1891.
- Kay, J.*: Original Portraits, Vol. I, Edinburgh, 1873, Adam and Charles Black, p. 330.
- Riddell, A., and Duffin, R.*: The Scots Magazine, p. 486, March, 1933.
- Simpson, A. R.*: Edinburgh M. J. 28: Part I, 1882.
- Idem*: Obst. J. Great Britain and Ireland, 45: Dec., 1876.
- Smellie, Wm.*: Treatise on Midwifery, Ed. A. H. McClintock, Vol. I, London, 1876-78, The New Sydenham Society, pp. 12, 23.
- Turner, A. L.*: History of the University of Edinburgh, 1888-1933. London, 1933, Oliver and Boyd.
- Young, Thomas*: Lectures on Midwifery. Edinburgh, 1771. Surgeon General's Library, 140865, 142749.
- Notes of students. *Young, Thomas*: Dissertatio Medica Inauguralis de Lacte, quam pro gradu doctoris eruditorum examini subjecit. Britannicus. Artis Obstetricae P. Edinburgh, 30 Novembris, 1761.

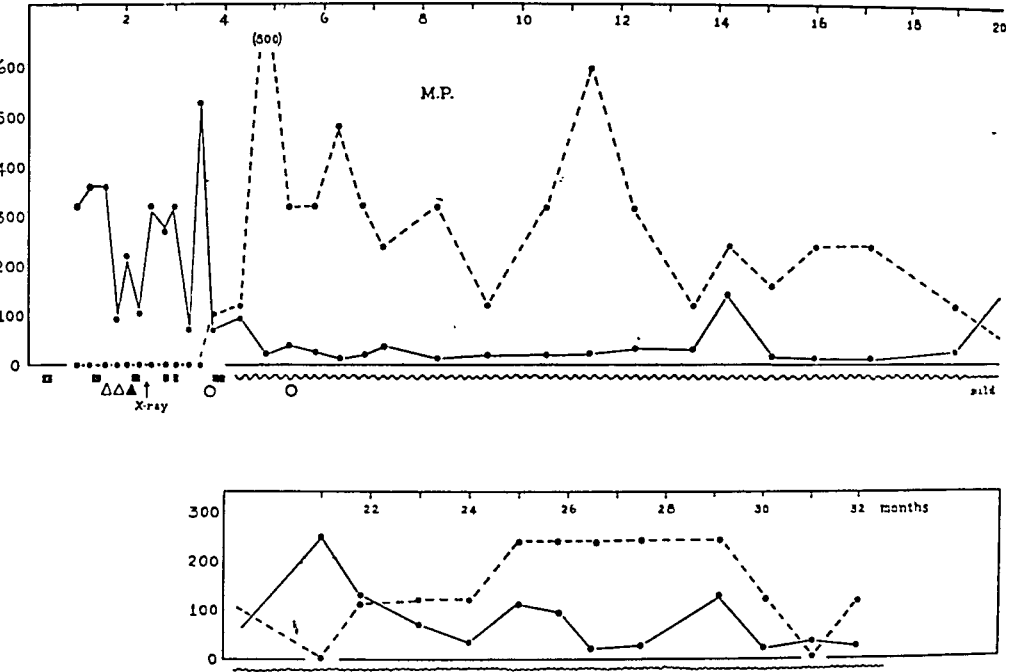


Chart 1.

Charts 1 to 5.—*Broken line*: Follicle-stimulating hormone in mouse units per twenty-four-hour specimen of urine. *Continuous line*: Total estrogens in international units equivalent to crystalline estrone. *Wavy line*: Hot flushes. *Solid block*: Menstrual period. *Open triangle*: Endometrial biopsy, proliferative phase. *Solid triangle*: Endometrial biopsy, secretory phase. *Circle*: Endometrial biopsy, secretory phase. *Ra*: Intrauterine radium. *H*: Hysterectomy and oophorectomy.

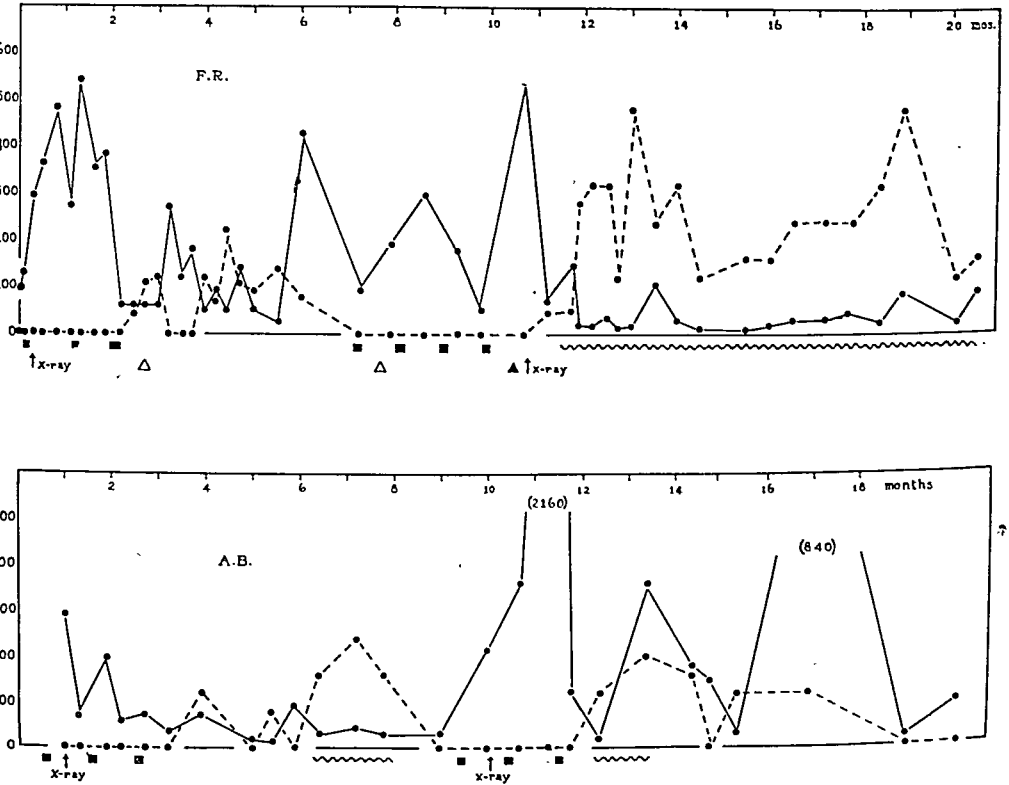


Chart 2.

tation of the urine with subsequent assay of the hormone on immature inbred black mice (Bar Harbor strain C57). Except in several instances no attempt was made to assay for follicle-stimulating hormone in titers of less than 80 M.U. per twenty-four-hour specimen. Methods published since the onset of this investigation are probably more accurate for the quantitative assay of follicle-stimulating hormone, but as far as we are aware none of the techniques available are capable of furnishing more than a relative index of the total hormone excretion of the gonadotropic hormones. This method has been found suitable for our purposes, since we were interested only in gross differences and did not consider values below 80 M.U. especially significant.

The technique of Smith and Smith³ was employed for extraction of the total urinary estrogens. This consisted of acid hydrolysis of the urine and subsequent extraction with benzol. Assay was then performed on spayed female adult black inbred mice (C57) according to a minor modification of the Allen-Doisy technique. This method is capable of detecting minute quantities of the hormone. The assays for both follicle-stimulating hormone and estrogen were carried out on complete twenty-four-hour specimens of urine, so that all figures presented represent the total daily output.

RESULTS

The charts shown were selected from the entire group of patients to present graphically the essential observations in this study. Of the points illustrated in these, the following are worthy of mention:

Following irradiation of the ovaries, although fluctuations did occur, there was a gradual diminution in the excretion of the urinary estrogens until a fairly constant level considerably below normal was reached. As the estrogen excretion decreased, follicle-stimulating hormone appeared in the urine at levels of 80 M.U. or higher per twenty-four-hour specimen (M.P., Fig. 1, M.S., Fig. 3, E.K., Fig. 5). In general, however, this titer was obtained only when the estrogen levels were exceedingly low. Occasionally it increased before that time, while the estrogen was still elevated, though below the normal level (F.R.) (Fig. 2).

Menopausal symptoms commenced within one to seven weeks after the detection of follicle-stimulating hormone, but most often within two to three weeks. It should be emphasized that the symptoms did not occur in the presence of low estrogen levels alone, but only when there was a relatively high titer of follicle-stimulating hormone. The above chain of events occurred more rapidly in the oophorectomized patient (A.W., Fig. 4) and less rapidly in the patient treated with radium (C.M., Fig. 4).

In three instances (F.R., Fig. 2, M.M., Fig. 3, and A.B., Fig. 2), the first attempt to produce permanent amenorrhea with roentgen treatment was unsuccessful although a temporary cessation of the menses occurred. Two of these patients (F.R. and A.B., Fig. 2) received another course of treatment which was followed by permanent amenorrhea and the symptoms of the menopause with the corresponding changes in the hormonal excretion. In the third patient (M.M., Fig. 3) who was near the climacteric, further treatment was refused. Later this patient had a permanent cessation of menstruation resembling that of a spontaneous menopause following several normal periods. Before the recurrence of her menses, there was a marked rise in the estrogen excretion and a decrease in follicle-stimulating hormone to levels below 80 M.U. per twenty-four-hour specimen, with a cessation of hot flushes. It was possible in these cases to predict a resumption of menses with a certain degree of accuracy because the hormonal titers were known.

The effectiveness of the roentgen ray treatment in producing castration as regards the age of the patient was also studied. Of 6 patients close to 40 years of age only 1 had a period after the treatment, whereas

of 6 patients close to 30 years of age, 5 had one or more periods. The time at which the therapy was instituted during the menstrual cycle bore no relation to the number of periods that followed or to the effectiveness of the therapy.

Endometrial biopsies taken before and after roentgen therapy yielded the expected findings until amenorrhea became permanent. Later attempts to obtain tissue were unsuccessful. In one instance an endometrial biopsy taken just before the expected menses showed a normal

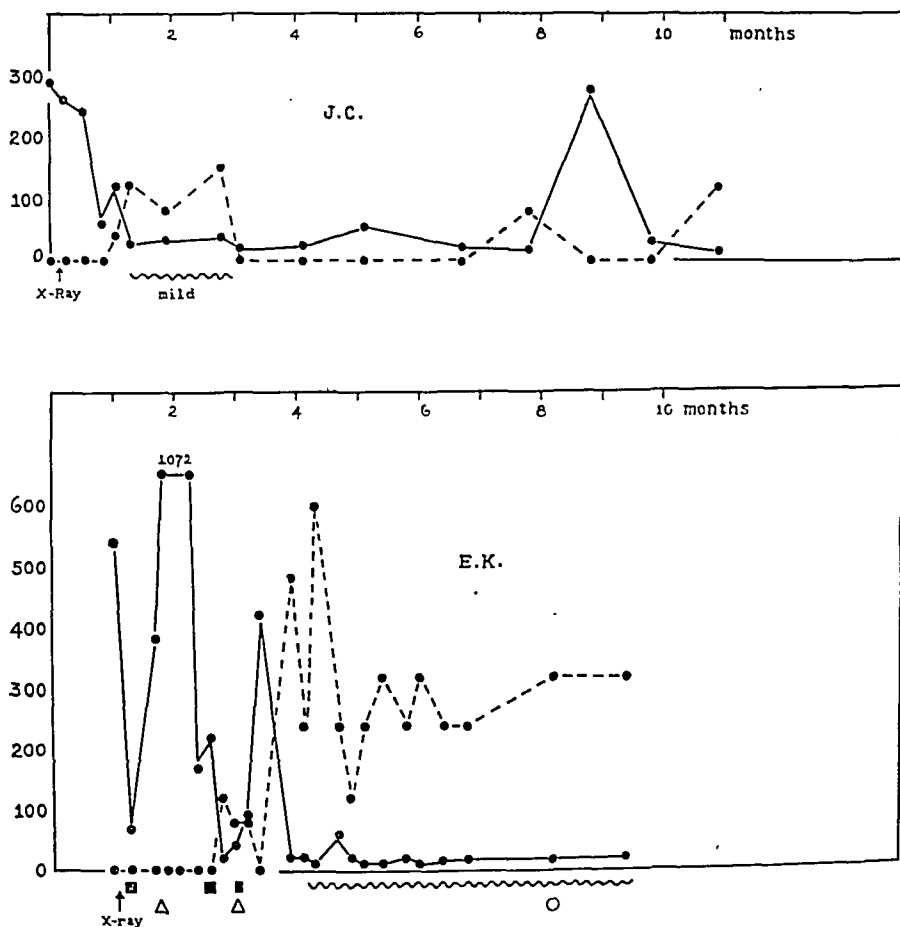


Chart 5.

secretory or functional endometrium and yet the period never materialized, indicating that cessation of menstruation can occur at any time in the cycle. The vaginal mucosa of these irradiated patients resembled those of women in the spontaneous menopause.

Observations on other roentgen castrates (10) one to three years after therapy, yielded findings similar to those shown in the charts. The urine of women assayed during the course of the spontaneous menopause and after its completion usually showed estrogen determinations well below normal. However, follicle-stimulating hormone was not recovered in elevated titers in every patient. The estrogen levels in several of these patients who had an excess of follicle-stimulating hormone, without vasomotor symptoms, were higher than those usually ob-

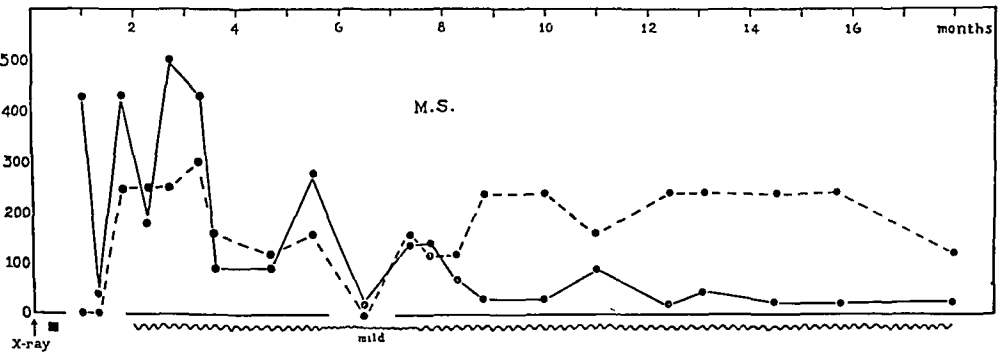
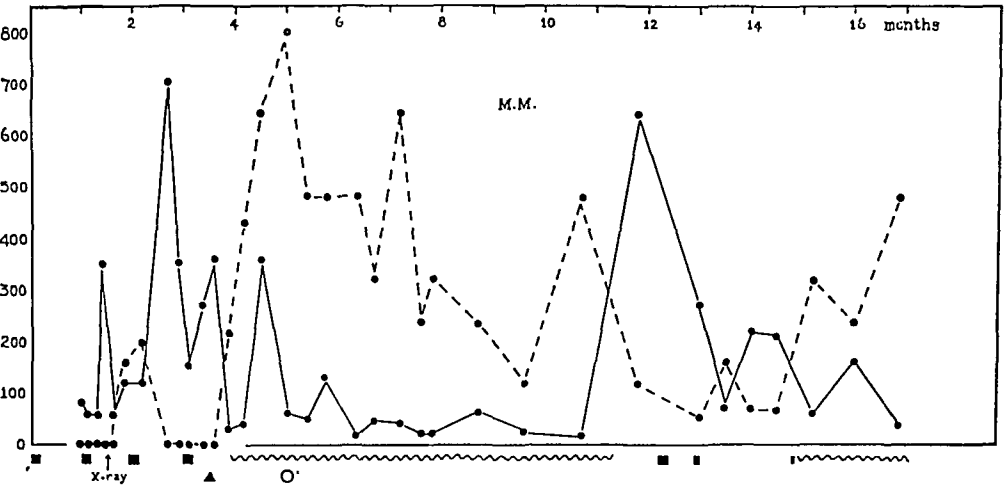


Chart 3.

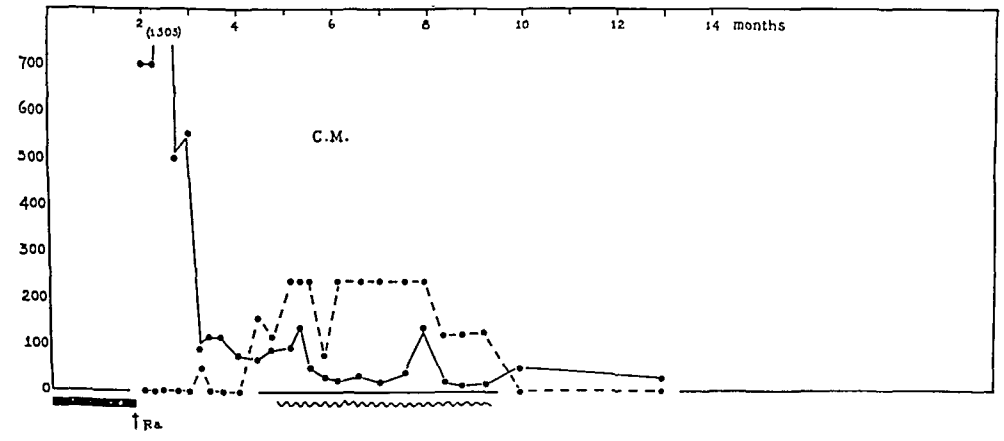
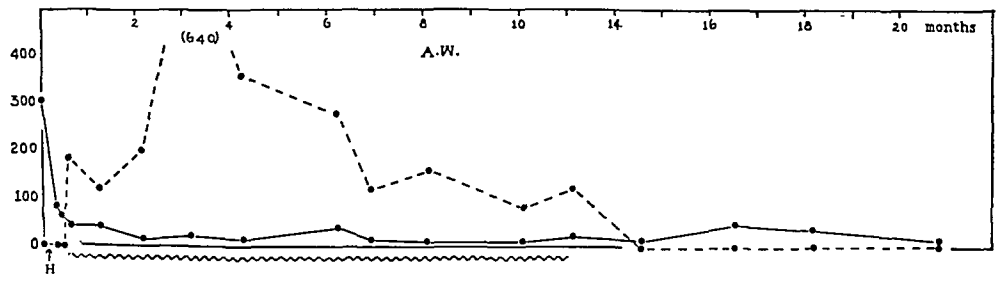


Chart 4.

pare these data. It is possible that the estrogen levels may account for the presence or absence of symptoms even though follicle-stimulating hormone may be present in sufficient quantities to evoke a response with our method (F.R. and A.B., Fig. 2). This may explain the difference in our findings. Our results indicate that symptoms were seldom present when the urine of the patients castrated by x-ray titrated less than 80 M.U. and that they were almost always manifested when the titers were above this level. It seems especially significant that no symptoms referable to the menopause could be detected before the first significant rise of follicle-stimulating hormone, and this suggests that the severity of the symptoms paralleled the levels. A recent study of Fluhmann and Murphy is in accord with this view of follicle-stimulating hormone.¹⁸ One of the cases in this series (J.S.) offers some evidence on this point. It can be seen that the follicle-stimulating hormone in the titer mentioned was recorded on a few occasions and only at this time did this patient have menopausal symptoms. Hot flushes were absent during the rest of the period of study although the estrogen levels were low and the patient amenorrheic. In this particular instance the pituitary gland apparently did not become very hyperactive as a result of castration, and this may explain the absence of vasomotor symptoms. Lassen and Brandstrup⁶ could not demonstrate the presence of gonadotropic hormone in all of their patients who were castrated by x-ray or operation. However, they did not assay for less than 400 M.U. per liter, so it is likely that the hormones were present in lesser amounts. The thesis of hyperactivity of the anterior pituitary as a direct cause or a necessary accompaniment of the menopausal syndrome is further substantiated by a study of the follicle-stimulating hormone levels (A.W. and C.M., Fig. 4) over a prolonged period after the symptoms had commenced. The follicle-stimulating hormone, although relatively high at first, gradually decreased, and later could seldom be demonstrated in the urine in titers of 80 M.U. or more. Accompanying the decrease there was a gradual diminution in symptoms which eventually ceased, thus coinciding with this decrease of follicle-stimulating hormone in the urine. This suggests that the gonadotropic function of the anterior pituitary in some patients fails gradually after its original hyperactivity. This is contrary to the findings of Heller and Heller who continued to find large amounts of gonadotropic hormone in the urine of all patients studied long after the symptoms had disappeared. The time required for the metamorphosis varies considerably in the individual patient, but the observations recorded suggest that the more abruptly the hyperactivity occurs the more rapidly it will cease. The symptoms are usually more severe in the group who have had an artificial menopause, but by the same token run a more rapid course and finally disappear. Analogous variations are manifested in the spontaneous menopause. The above findings conform to those of Albright⁷ and support his contention that the important change in the menopause may be a hyperactivity of the anterior pituitary subsequent to ovarian failure.

tained in the menopause. It is also interesting that estrogens were recovered from urine of every patient studied, including the surgical castrates even though the symptoms pointed to cessation of ovarian activity.

DISCUSSION

These studies suggest certain possibilities which necessitate discussion and analysis. Following ovarian irradiation there is a gradual diminution in the urinary estrogen excretion. This is probably due to a direct action upon the follicles as a result of which their activity is suppressed. As follicle secretion decreases following x-ray therapy, the anterior pituitary becomes hyperactive which is manifested by an increased urinary excretion of follicle-stimulating hormone. (Follicle-stimulating hormone in excess in the menopause and after castration was reported by Zondek,⁴ and since that time many workers have made the same observation.) Shortly after this the vasomotor symptoms of the menopause appear, but these symptoms are not an accompaniment of low estrogen levels alone, for they seem to be present in most instances only when follicle-stimulating hormone is found in titers over 80 M.U. per twenty-four-hour specimen. This suggests that a certain degree of hyperactivity of the anterior pituitary must exist before symptoms appear. The appearance of these vasomotor symptoms only after the first significant rise in follicle-stimulating hormone, as shown by Albright⁷ and by these studies, suggests that hyperactivity of the anterior pituitary is a necessary accompaniment of the symptoms if not the exciting cause. It must be stressed, however, that some factor in the pituitary other than follicle-stimulating hormone may be responsible for the symptoms, for in our opinion the increase in follicle-stimulating hormone merely indicates an hyperactivity of the anterior pituitary gland. It is probable that this may also be shown by assay of other tropic factors. Heller and Heller⁵ in a recent study could find no relationship between the gonadotropic potency of the urine and the presence or absence of menopausal symptoms in various types of patients. Our studies on women with a spontaneous menopause partially confirm these results. Although we frequently found elevations of follicle-stimulating hormone in the absence of symptoms, these levels were usually below those detected when vasomotor reactions were apparent. In the presence of symptoms, however, we seldom failed to recover follicle-stimulating hormone in fairly high titers.

In contradistinction to the patients with spontaneous menopause, the laboratory findings in the group reported in this study seem to be fairly well correlated with the clinical symptoms. We made no attempt to assay for quantities of follicle-stimulating hormone less than 80 M.U. per twenty-four-hour specimen since we considered only gross variations as significant. It is possible that the method employed is less sensitive than that utilized by Heller and Heller. The precipitation method in both studies is identical. It differs only in the technique of assay and in the attempt to detect minimal amounts of the hormone. Since they did not carry out assays of the urine for the estrogen, we cannot com-

strated that with insufficient irradiation many of the primordial follicles were not destroyed, continued to mature and were active, since the estrous cycle was maintained. It also seems apparent that the estrogens must reach a certain threshold before the elevated follicle-stimulating hormone levels become lowered and the vasomotor symptoms are alleviated or cease entirely. This is shown in the graphs of those patients who resumed menstruation after a period of amenorrhea induced by x-ray. One may conclude from these observations that resumption of the menses depends upon the activity of the ovary and its ability to respond sufficiently to a stimulus, since a high level of estrogen was found to be necessary before menstruation recurred.

The efficiency of roentgen treatment as a means of producing the necessary changes in the ovary to bring about the menopause was demonstrated in the ovaries of one woman who came to autopsy three years after the treatment. Grossly, the ovaries were shrunk and fibrotic. Microscopically the follicles were destroyed, and there was connective tissue replacement. The report of Dr. Shields Warren follows:

"The ovary presents the picture of an atrophic, postmenopause organ. The cortex is narrow, containing one or two scars but not follicles. In the medulla are numerous corpora albicantes. There is moderate hyalinization of the arteries."

The age of the patient, however, has some bearing on the ease with which the ovaries may be destroyed. This is to be expected since the follicles of the ovaries of the younger group are more numerous and probably more active than those of the older group. In general, it may be stated that large dosages should be employed to effect sterilization of the ovaries in the younger age group.

The fact that estrogens were recovered in every specimen of urine from the patients studied, including the surgical castrates, confirms the work of Frank and others;¹³ La Roche and others;¹⁴ Fluhmann;¹⁵ Eng;¹⁶ and others. Kurzrok,¹⁷ Albright,⁷ and others found no estrogens in the urine when follicle-stimulating hormone was present. With improved methods, however, in the extraction of the estrogens our findings can be reconciled to theirs, since the earlier methods were not delicate enough to detect minimal amounts of the estrogenic hormone. Hence, these findings suggest an extragonadal source of estrogens especially in the case of the surgical castrates. The adrenals are a possible source of estrogenic hormones if the ovarian follicles are completely suppressed, but proof for this is at present lacking.

These studies indicate that the menopause has occurred and can be produced artificially when desired, by the use of x-ray or radium, as efficiently as by surgery. It is our opinion that there is no essential difference in the menopause produced artificially from that which occurs spontaneously, with one exception; i.e. the severity of the symptoms and the rate at which it is produced and runs its course. Of the artificial methods surgery is the most rapid, with x-ray and radium following in the order named. Any of these methods have their analogies in the spontaneous menopause and eventually all lead to the same end.

This study further demonstrates the pituitary-ovarian relationship. It indicates that normally a balance exists between the hormones of these glands, an alteration in which may give rise to various symptoms and findings which do not occur under normal conditions. In the presence of normal or large amounts of estrogen in the urine, follicle-stimulating hormone was seldom recovered in quantities of over 80 M.U. per twenty-four-hour specimen. Conversely in our experience a low estrogen and elevated follicle-stimulating hormone was usually found in patients with a spontaneous or artificial menopause. We cannot explain therefore the apparent paradoxical presence and relative elevation of both estrogen and follicle-stimulating hormone levels which were found on several occasions. This phenomenon has also been described by Albright⁷ and by Englehart and Tscherne.⁸

The behavior of the patients who resumed menstruation in spite of roentgen treatment of the ovaries seems worthy of comment. In these women the size of the x-ray portal was 10 by 10, distance 50 cm., and the total dosage delivered was 1,200 r. given in four divided dosages anteriorly and posteriorly, through one field in each region. In the others, the portal was 15 by 15 and the dosage varied from 1,200 to 1,600 r. With the latter dosage the skin target distance was 77.5 cm. It is probable that in the three unsuccessful instances the dosage was not sufficient nor the portals large enough to permanently destroy or damage all the follicles. This is clearly illustrated in the case of F.R. where the estrogen excretion fluctuated considerably but never reached a constant level until a second course of treatment was given after menses had returned. In these cases in which the treatment was apparently inadequate the cessation of hot flushes, the rise in the urinary estrogens, and the decrease in follicle-stimulating hormone anticipated the reappearance of the menses. When menstruation did recur a normal rhythm was resumed and the first catamenia after the period of amenorrhea came at the time it would have been expected. This finding suggests that a pituitary rhythm exists even in the absence of menstruation. Smith and Smith⁹ have suggested that this rhythm continues throughout pregnancy and one of us (I.T.N.¹⁰) in an experimental study of inhibition of the estrous cycle in the rodent has noted a similar phenomenon. In some of our patients who had a permanent amenorrhea, there were fluctuations in the follicle-stimulating hormone and estrogen levels throughout the period of study. There were drops in follicle-stimulating hormone and rises in the estrogens, but at no time did the levels constantly approach those of women who menstruate. Watson and others¹¹ suggest that at the menopause the ovaries gradually become refractory to stimulation by the gonadotropic hormones. The degree of response to stimulation must vary considerably. It is reasonable to assume that in these instances there is incomplete destruction of the follicles so that, although fluctuations do occur, the normal menstrual rhythm is not re-established because of the inability of the ovary to respond sufficiently to the pituitary stimulus. This concept is in accord with the experimental findings of Genther¹² in her study on guinea pigs. She demon-

THE RECOGNITION AND TREATMENT OF FETAL HEART ARRHYTHMIAS DUE TO ANOXIA*

CURTIS J. LUND, M.S., M.D., MADISON, WIS.

(From the Department of Obstetrics and Gynecology, University of Wisconsin, and the State of Wisconsin General Hospital)

THE rate and rhythm of the fetal heart constitute the most satisfactory if not the only direct method for constant study of the physiology of the fetus during pregnancy and labor. Accurate interpretations of variations are as yet incomplete; nevertheless, auscultation provides evidence of impending fetal danger when marked arrhythmias are present. Fetal anoxia, infrequently recognized and rarely treated antenatally, can quickly produce grave fetal complications. The old therapeutic dictum "prophylaxis is the prime treatment" has not received significant consideration by obstetricians when signal variations of fetal heart rate foretell subsequent disaster. Careful and constant auscultation and recording of the fetal heart rate are the best criteria available for study of the unborn infant during labor.

Mayor¹ and Kergaradec³ working independently first described the fetal heart sounds in 1818 and 1821, respectively, though Fasbender² gives credit to LeGoust in 1650. Kennedy,⁴ Naegele,⁵ and Hohl⁶ first realized the prognostic importance of variations in fetal heart rate. Later Cummings⁷ emphasized the danger associated with irregular or weak heart sounds. Von Winckel⁸ in 1893 believed asphyxia imminent when the rate exceeded 160 or decreased below 100 and that expedient delivery was indicated. More recently other observers have arrived at similar conclusions. Included are Reed,⁹ Sachs,¹⁰ Frey,¹¹ Bartholomew,¹² Freed,¹³ and many others.

Satisfactory reproduction and recording of the fetal heart rate is a comparatively recent accomplishment though first attempted by Hofbauer and Weiss¹⁴ in 1908. The most recent study has been reported by Smith and Hervet¹⁵ who have reviewed the literature and report the technical data concerning the study of the normal fetal heart.

APPARATUS AND METHODS

For the present investigation auscultation and recording of the fetal heart rate were accomplished with the endocardiograph;† a cardiograph devised for auscultation and recording of heart sounds, but readily applied to auscultation of fetal heart sounds with no significant change in apparatus. The sounds are picked up by a crystal microphone, amplified, and then may be heard by means of a binaural stethoscope or loud-speaker, or recorded on a moving strip of paper by a writing pen. The paper moves at a constant speed of one or two inches per second as desired. When at certain times the endocardiograph has not been available or desired, the fetal heart rate has been recorded by use of the head stethoscope or the weighted Leffscope¹⁶ and a stop watch. During early first stage of labor, the fetal heart rate is observed every fifteen minutes or oftener if indicated; during the last portion of the first stage and the entire second stage, continuous auscultation is carried

*Aided by a grant from the Wisconsin Alumni Research Foundation, Madison, Wis.

†The endocardiograph is manufactured by the Endocardiograph Company, Milwaukee, Wisconsin.

CONCLUSIONS

1. The artificial menopause can be considered analogous to the spontaneous menopause, the major difference being the rate at which the climacteric is finally reached.
2. X-ray, if properly used with adequate-sized portals and dosage, is as efficient in producing the artificial menopause as surgery.
3. The success of castration with radiation depends to some extent upon the age of the patient.
4. Assay of the urine for follicle-stimulating hormone and estrogenic substances and endometrial biopsies give valuable information as to the effectiveness of radiation castration in the individual case.
5. Vasomotor symptoms of the climacteric are accompanied by hyperactivity of the anterior pituitary.
6. Elevated levels of follicle-stimulating hormone may be found in the absence of vasomotor symptoms, but on the other hand elevations in follicle-stimulating hormone are almost always detected in the presence of these symptoms.
7. Estrogenic substances exert an inhibiting effect on the action of the anterior pituitary gland.
8. There is probably an extragonadal source of estrogens.

REFERENCES

- (1) *Taylor, G. W.*: Am. J. Roentgenol. 39: 419, 1938. (2) *Dresser, R.*: Ibid. 35: 384, 1936. (3) *Smith, G. V., and Smith, O. W.*: Am. J. Physiol. 112: 340, 1935. (4) *Zondek, B.*: Ztschr. f. Geburtsh. u. Gynäk. 90: 372, 1926. (5) *Heller, C. G., and Heller, E. J.*: J. Clin. Investigation 18: 171, 1939. (6) *Lassen, H. C. A., and Brandstrup, E.*: Acta obst. et gynec. Scandinav. 14: 89, 1934. (7) *Albright, F.*: Endocrinology 20: 24, 1936. (8) *Englehart, E., and Tscherne, E.*: Zentralbl. f. Gynäk. 60: 790, 1936. (9) *Smith, G. V., and Smith, O. W.*: New England J. Med. 215: 908, 1936. (10) *Nathanson, I. T., and Fevold, H. L.*: Endocrinology 22: 86, 1938. (11) *Watson, B. P., Smith, P. E., and Kurzrok, R.*: AM. J. OBST. & GYNEC. 36: 562, 1938. (12) *Genther, I. T.*: Am. J. Anat. 48: 99, 1931. (13) *Frank, R. T., Goldberger, M. A., and Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 33: 615, 1936. (14) *La Roche, G., Simonnet, H., and Huet, J. A.*: Semaine d. hôp. de Paris 12: 405, 1936. (15) *Fluhmann, C. F.*: AM. J. OBST. & GYNEC. 32: 612, 1936. (16) *Eng, H.*: Klin. Wehnschr. 15: 349, 1936. (17) *Kurzrok, R.*: Endocrinology 16: 366, 1932. (18) *Fluhmann, C. F., and Murphy, K. M.*: AM. J. OBST. & GYNEC. 38: 778, 1939.

Ritala, A. M.: On the Inheritance of the Parents' Constitution by the New-Born Child, Ann. inst. obst. et gynec. Universitatis. 11: 1, 1939.

Length and weight of body as well as head circumference of mother, father, and newborn child were studied by Ritala. In all, 12,860 body measurements of parents and newborn children were taken.

The weight and length of the newborn child proved to be considerably less, dependent upon the corresponding body measurements of the child's father, than upon those of the mother.

The results attained emphasize the comparatively great importance of heredity in opposition to the slight influence of environment or the mother's age, to which too great importance has been attached in the past. Besides inheritance, the sex of the fetus and the number of the mother's deliveries have been proved to exercise a decided influence on the body development of the newborn child.

TABLE I. OBSTETRIC STATUS AT THE TIME OF ONSET OF ANOXIC SLOWING OF FETAL HEART AND THE RESPONSE TO OXYGEN THERAPY

	POSITION	STATION	DILATATION	MEMBRANES RUPTURED	TYPE OF CONTRACTIONS	DURATION OF CONTRACTIONS (SEC.)	MINUTES BETWEEN CONTRACTIONS	MATERNAL CYANOSIS	SPONTANEOUS RESPIRATIONS	ASPHYXIA	CORD AROUND NECK	FETAL HEART RATE					RELATION OF ONSET TO ANALGESIA
												BEFORE ANOXIA	WITH ANOXIA	DURATION OF SLOWING (MIN.)	AFTER OXYGEN THERAPY	RECOVERY (COMPLETE) TIME (MIN.)	
1-UG	S.L.T.	-1	6	Yes	Str.†	60	3	+	Yes	No	No	156	68	15	150	15	Before
2-EE	L.O.A.	+3	C*	No	Str.	60	1	-	Yes	No	Yes	140	70	8	135	8	With
3-SE	L.O.A.	0	C	No	Mod.†	45	2	+	Yes	No	No	136	110	4	140	8	After
4-RH	L.O.A.	+2	C	Yes	Str.	60	1½	-	Yes	No	Yes	116	98	13	120	10	With
5-VA	R.O.P.	0	0	No	—	—	—	+	Yes†	No	No	142	96	15	140	7	With
6-RN	L.O.A.	+1	4	Yes	Mod.	45	3	-	Yes	No	Yes	144	110	10	130	5	After
7-EF	S.L.A.	+3	C	Yes	Str.	50	2	-	Yes	No	No	140	to 130	15	to 140	15	With
8-EW	L.O.A.	+1	8	Yes	Mod.	50	3	-	Yes	No	No	142	to 134	8	to 144	12	With

*C, signifies complete dilatation of cervix.

†Patient not in labor at this time but delivered three days later.

‡Str., strong contractions. Mod., moderate contractions.

out. Recordings are frequently taken and all significant changes of fetal heart rate recorded. The fetal heart rate was noted at the end of a contraction and during the middle and late interval. Because of occasional minor rate changes, 5 to 10 beats per minute, not infrequently noted in the early interval, the recorded rate was made during the late interval. The rate was obtained from 30 second counts, shorter periods of counting may lead to rather great errors because of the rapid rate of the normal fetal heart. When greater variation than 5 to 10 beats per minute was present, it was noted. Along with the usual obstetric abdominal and rectal examinations careful and frequent observations were made of the type and severity of the contraction, the duration of the contraction and the interval between contractions. Furthermore, all cases were personally observed and recorded throughout, the importance of this is obvious but actually becomes a necessity during the period of continuous auscultation when readings require the entire attention of one individual. The anesthetic agents and gases were administered by members of the Department of Anesthesia, all of whom are trained, experienced anesthetists. The method of oxygen administration depended upon anesthetic technique. Any of the common standard techniques is satisfactory, provided adequate concentrations of oxygen reach the alveoli of the lung.

As has been mentioned, the slowing of the fetal heart rate has long been considered a sign of developing fetal asphyxia. Likewise, knowledge concerning the need for adequate oxygenation of the fetus to prevent apnea at time of delivery is of long standing and many have recognized the fact that oxygen could be administered to the mother in order to reach the infant.¹⁷⁻²⁰ To Waters and Harris²¹ must go the credit for emphasizing the fact that anoxia of the fetus can be recognized by change in the fetal heart rate and successfully treated by oxygen administration, thereby forestalling development of respiratory depression due to anoxia.

The importance of this observation has never been fully appreciated, and for this reason we have added a series of carefully studied cases, recently observed, which demonstrate the changes in fetal heart rate due to anoxia. With the perfection of auscultatory and recording devices we can now present objective evidence of these arrhythmias. It is not uncommon to observe term pregnancies, with fetal arrhythmia definitely due to anoxia. Eight cases have been chosen because each demonstrated slowing of the fetal heart due to anoxia and the therapeutic response to specific therapy, oxygen. Irregularities of fetal heart rate due to all other causes have been deliberately deleted from this report and will be considered in subsequent publications. This includes the other very important factor of asphyxia, carbon dioxide.

RESULTS

Table I summarizes the data regarding the condition of the patient at the time of the onset of fetal heart changes. From this it can be seen that many factors have been eliminated as individually etiologic, such as position, presentation, state of membranes and type of contractions and, furthermore, that anoxia can be present

was 140. Later cyanosis again followed obstruction, immediately the fetal heart rate decreased from 140 to 120. Correction of the obstruction relieved the cyanosis and the fetal heart rate increased to 136 within five minutes. The rate remained constant at 130 to 136 for twenty minutes until delivery.

MRS V.G

RATE 160



10³⁰ p.m

Before anoxia

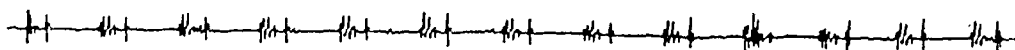
11⁰⁰ p.m



RATE 70

BEFORE O₂

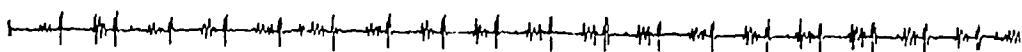
11⁰³ p.m



RATE 95

After O₂ for 3 minutes

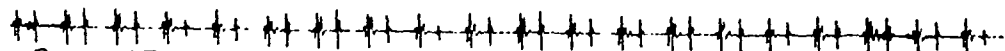
11¹⁰ p.m



RATE 137

AFTER O₂ for 10 min.

11²⁵



RATE 150

After O₂ for 25 min

Fig. 1.—Normal fetal heart rate of 160 followed by marked slowing to 70 due to anoxia. Response to oxygen present in three to five minutes with complete recovery in twenty-five minutes.

CASE 5.—V. A., a primipara, at term, not in labor, was to be examined under anesthesia. Nitrous oxide was chosen to demonstrate the slowing of fetal heart rate that follows use of too high concentrations of nitrous oxide and insufficient oxygen (Fig. 4). Normal fetal heart rate was 142, within ten minutes the rate had decreased to 96 during period of induction of anesthesia, after stabilization an optimum rate of 105 was obtained under nitrous oxide anesthesia, slight maternal cyanosis being present at this time. With addition of oxygen and change to another anesthetic agent, permitting greater concentrations of oxygen, the fetal heart rate returned to a normal rate of 140.

whether the patient is in labor or not. From this we do not mean to say that any of these given factors is not without effect in certain instances or entirely etiologic at other times.

Table I also summarizes the gross changes found in the fetal heart rate, the duration of arrhythmia before and after oxygen therapy, and the condition of the infant at the time of delivery. In order to eliminate any cases showing sudden transient changes in fetal heart rate which frequently correct themselves, it has been a rule to allow the slowing to persist for a minimum of ten minutes, if possible without danger to the fetus, or through at least three-interval periods between contractions. The time interval given for complete recovery signifies the time elapsed in minutes before recovery had reached its maximum point, which in most cases was a return to the original rate. The effect of oxygen, as will be seen later, can frequently be demonstrated within three to five minutes, the longest latent period was eight minutes. In every case respirations and cry were spontaneous, and there were no signs of anoxia or apnea at birth.

A short summary of the most significant and illustrative cases will serve to emphasize the various factors involved in producing fetal anoxia with arrhythmias and recovery after oxygen therapy.

CASE 1.—V. G., a very obese multipara, 40 years of age, weighed 256 pounds. Hypertensive heart disease was present with a blood pressure of 180/110. At bed rest she was neither dyspneic nor cyanotic. However, on very slight exertion dyspnea became marked. Labor was slow and difficult because of breech presentation and marked angulation of the uterus through a ventral hernia. Onset of slight dyspnea was noted after four hours of labor; however, there was no change in fetal heart rate which persisted at 150 to 160 for the following five hours. At this time dyspnea became marked and slight cyanosis could be seen. The fetal heart rate decreased to 135 and then to 70. This rate persisted constantly for over ten minutes. Cervical dilatation was 6 cm. and the breech was not engaged. At this time the patient was allowed to breathe a high concentration of oxygen through a face mask. Within three minutes the rate had increased to 95, after five minutes the fetal heart rate was 120, after ten minutes was 135, and after twenty-five minutes 148 (Fig. 1). Similarly there was improvement of maternal dyspnea and cyanosis after ten minutes of oxygen therapy. After twenty minutes respirations were normal, and after thirty minutes the maternal pulse rate had decreased from 120 to 100. Good pain relief was obtained from nitrous oxide oxygen and cyclopropane analgesia and no further slowing of the fetal heart rate occurred. The cervix was allowed to dilate, and delivery was accomplished two hours after the original onset of fetal heart slowing. The infant was in good condition at birth.

CASE 2.—E. E. The fetal heart rate in this young primipara during the last part of the first stage and the early second stage of labor remained within the limits of 140 and 148. It was unaffected by nitrous oxide (70 per cent) oxygen (30 per cent) analgesia for thirty minutes. At this time due to increased severity of pains, the nitrous oxide was increased to about 85 per cent. This diminution of oxygen supply plus the increased need due to muscular effort in bearing down caused a slowing of the fetal heart rate within four minutes to 120, and within eight minutes to 70 (Fig. 2). At this point, without any other change in obstetric or anesthetic procedures, the patient was given oxygen during the interval between contractions. Within two minutes the rate reached 90 at the end of a contraction. After six minutes the rate was 105, after eight minutes 135, with only a very slight slowing to 128 immediately after a contraction. This improved rate persisted and spontaneous delivery of a normal infant in good condition followed one-half hour later.

CASE 3.—S. E., a primipara, in the second stage of labor, was being examined under cyclopropane-oxygen anesthesia. The fetal heart rate before anesthesia was constant within a range of 132 and 136. During the first five minutes of anesthesia, it remained between 136 and 140 (Fig. 3). At this time large amounts of mucus accumulated, causing respiratory obstruction with rather marked cyanosis. Fetal heart rate reached a low of 110, at the time the respiratory obstruction was corrected. The rate improved to 126 within eight minutes and after eleven minutes

rate for the entire remaining minute of the interval. The infant was born in good condition twenty minutes later.

DISCUSSION

The occurrence of arrhythmias of the fetal heart during labor is far more frequent than is generally believed. This is probably due to infrequent and inaccurate auscultation. Of these arrhythmias, due to

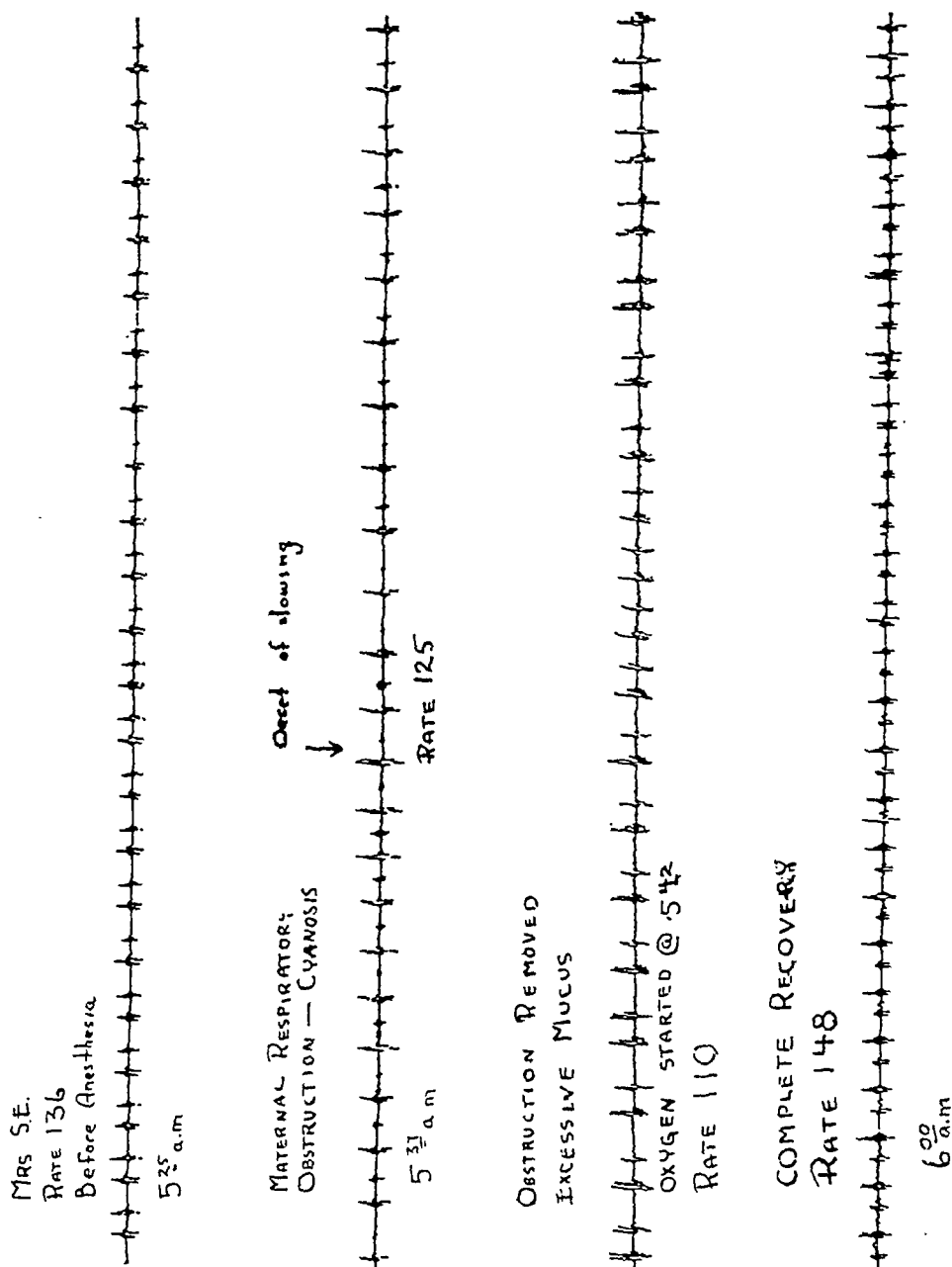


Fig. 3.—Slowing of fetal heart rate from anoxia due to maternal respiratory obstruction by excess mucus. Aspiration of mucus and establishment of good airway resulted in recovery.

anoxia in utero, those that can be corrected by administration of oxygen to the mother constitute a far greater group than many obstetricians and anesthetists realize. From the vast literature of recent years, several definite clear-cut facts have been determined concerning the signs and sequelae of oxygen want. In adults mild degrees of anoxia are followed

CASE 7.—E. F., a primipara, with breech presenting, was in the second stage of labor. A slowing of fetal heart rate was noted shortly after nitrous oxide analgesia was instituted. Within ten minutes the rate was 100, immediately after a contraction, and the slowing persisted throughout all but the final fifteen or twenty

Mrs I. I.

6²⁵ p.m.

RATE 140



Nitrous Oxide

Analgesia

6³⁴ p.m.

RATE 70



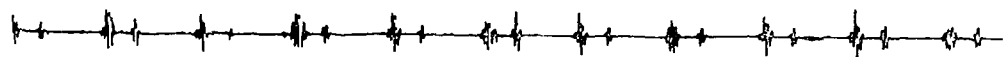
BEGIN CONSTANT

OXYGEN BETWEEN

CONTRACTIONS

6³⁷ p.m.

RATE 90



3 minutes after
Oxygen increase

6⁴⁰

RATE 105



6 minutes after Oxygen

6⁴²

RATE 135



NORMAL 8 min. after O₂

Fig. 2.—Slowing of fetal heart rate under nitrous oxide analgesia corrected by administration of oxygen during the interval between contractions.

seconds of the two-minute interval, when it rose to 130. At this time oxygen was given between contractions. Within fifteen minutes, the rate, while still 100 immediately after a contraction, recovered to 135 within one minute, leaving a normal

Schreiber²⁵ who also describe "devastation areas" in the cortex of infants dying of asphyxia.

Most authors state that the first sign of fetal asphyxia is an acceleration of the fetal heart rate and as asphyxia deepens the rate slows markedly, just as has been described for adults. We have failed to note acceleration of the heart rate in any of the cases of this series. Just why the fetal heart does not consistently respond to anoxia by acceleration is not known. Perhaps it is masked by other factors such as the rapidity of the development of the anoxia or the degree of anoxia present. Snyder and Rosenfeld²⁶ discovered that intrauterine respirations of the fetus were not stimulated by mild anoxia as in the adult individual. The mechanism involving the fetal heart rate and respiratory rate may be similar in nature, for we know that both respiratory rate and pulse rate are stimulated by mild degrees of anoxia in the adult.

In the same year that Waters and Harris²¹ reported successful therapy of anoxic infants in utero with slow fetal heart rate, Rech²⁷ reported that he had given patients, in labor, increased concentrations of oxygen without effect on fetal heart rate. He also reported that exposure to a low oxygen content of inspired air for one and one-half minutes was without effect on the fetal heart rate. The development of significant anoxia in utero in our experience is not ordinarily accomplished in the short time of one and one-half minutes. In Case 3 rather marked maternal oxygen want was present for five minutes before effect was noted on the fetal heart rate. This lag in response is not remarkable when the complexity of the transporting system is considered. Involved are the circulation time through the uterus, the oxygen saturations in the placenta, and the circulation time of the fetus. The latter alone has been found to be about forty seconds.³⁶

There are two broad factors involved in the production of anoxia of the fetus, maternal failure to supply oxygen, and failure of the fetus to receive a proffered supply.

1. *Failure of Maternal Supply.*—This includes a list so great that its limits would be bounded only by the ingenuity of the enumerator. For a general classification of anoxia the accepted group suffice: (1) Anoxic, (2) stagnant, (3) anemic, and (4) histotoxic. Yet it must be appreciated that nearly every case under consideration may, and usually does, involve a combination of several of these factors.

Failing or inefficient respiration (anoxic anoxia) probably represents the major etiologic factor in most of these cases. The significance of the relatively low oxygen concentration of anesthetic mixtures of nitrous oxide has been discussed for many years. Positive proof that anoxia follows the use of certain mixtures of nitrous oxide and oxygen was revealed by Leake and others,²⁸ Waters and others.³⁰ In Eastman's³¹ studies definite fetal anoxia was produced by administration of nitrous oxide oxygen in concentrations of 90:10 for longer than five minutes. Danforth and Davis¹⁸ noted a slowing of the fetal heart rate during deep gas (nitrous oxide oxygen) anesthesia which resembled those heard in asphyxia. Smith³² reported fetal anoxia during delivery under cyclo-

by acceleration of the pulse and respiration. If the anoxia persists or increases, the point of "oxygen crisis" is reached. Schmidt²² calls the subsequent period the "reversal" in which the heart rapidly slows to

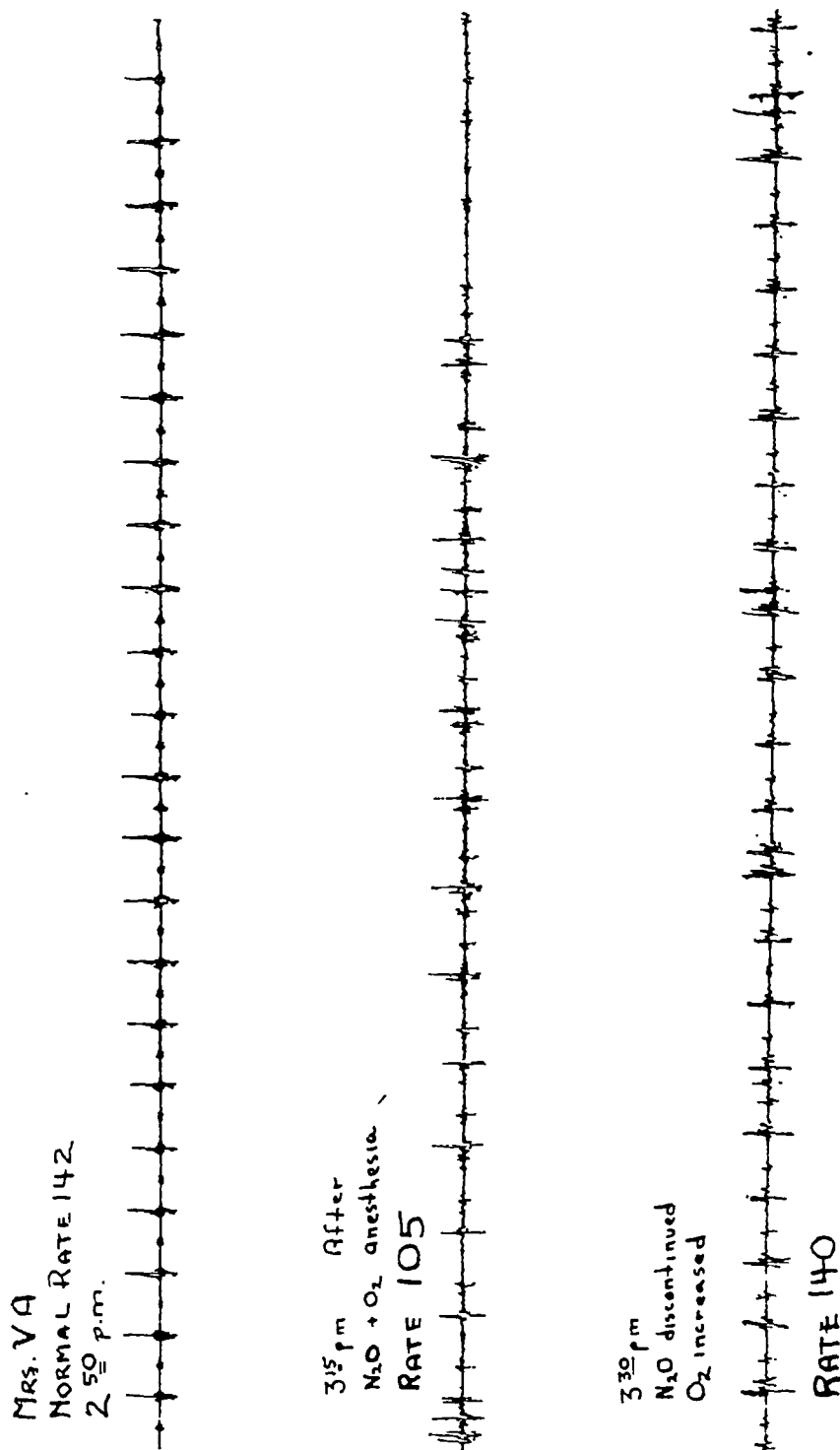


Fig. 4.—Complete anesthesia (first plane) with nitrous oxide required the reduction of oxygen to a point below physiologic needs with resulting anoxia and slowing of the fetal heart rate.

about 40 or 45. Vagal stimulation is apparently the cause for the slowing of the heart rate. Persisting anoxia in the adult is followed by serious cerebral damage as noted by Yant and others,²³ Courville²⁴ and

Census. With complete obstruction of the cord, asphyxia is inevitable; not so, however, with intermittent cord pressure and cord entanglement. In these cases, the obstruction may be complete at the time of uterine contractions, giving a slow fetal heart rate during the interval. If oxygen is given in large amounts between contractions, the enriched maternal blood supply is capable of restoring the infant, and improvement is noted. This was noted in Case 8 in Table I. While it is not advisable to delay treatment in cases of cord prolapse, nevertheless high concentrations of oxygen should be given while preparing for expeditious delivery.

Recognition of intrauterine anoxia is generally dependent on a slowing of the fetal heart rate, either in the form of a rather sudden change of 25 or more beats per minute or a persistent slowing below 100 and 110. This is of greater significance, should any of the previously mentioned etiologic factors be present. The diagnosis may be considered positive, should the therapeutic response to oxygen be obtained. Obviously the converse is not true, for all cases of fetal anoxia do not respond to maternal oxygen therapy.

In general, the response to oxygen therapy is rapid and at times dramatic. In every case of the series, there was improvement within five minutes after therapy was begun and maximum recovery was reached within twelve to twenty minutes. This fact is of clinical importance, because on most obstetric floors, at least ten minutes elapse before the patient can be prepared for immediate delivery, should it be possible and elected because of slowing of the fetal heart rate. During this time the anesthetist can be giving the therapeutic test of oxygen. Improvement should be noted within ten minutes after administration and frequently will be seen within five minutes. Failure of any response within ten minutes is significant, and a persistent fetal heart rate below 100 indicates that response to oxygen will probably not be seen and delivery should not be delayed. If delivery is impossible consideration should be given to deep anesthesia with simultaneous continuation of oxygen concentration at a high level. The fact that nitrous oxide was involved in several of these cases does not condemn the use of the gas as an analgesic agent or even as an anesthetic agent for a short period of time. Of great importance is the fact that high concentrations of oxygen may be given to the patient during the intervals between contractions to relieve a fetal anoxia that may occur during the fifty to seventy seconds of nitrous oxide analgesia.

SUMMARY

The literature is replete with methods and devices to treat asphyxia of the newborn. The value of this therapy cannot be disregarded or minimized and yet in many cases the opportune time for therapy has passed and irreparable damage to the central nervous system is the unfortunate result. Variations of the fetal heart rate have long been ascribed to asphyxia and the recommended therapy has been immediate delivery. The early recognition of impending fetal asphyxia can be

propane anesthesia when maternal oxygenation was good. During the past year, our data, as yet insufficient and inconclusive, tend to confirm this observation as demonstrated by a slowing of the fetal heart rate in deeper planes of cyclopropane anesthesia, but not so with ether. Slowing of the fetal heart rate under anoxic conditions associated with nitrous oxide oxygen anesthesia can be readily and repeatedly demonstrated and recorded (Fig. 4).

Fetal anoxia produced by obstruction to the maternal respiratory passages should be prevented or immediately relieved by correction of such impediments. This was very vividly demonstrated and recorded during our studies (Fig. 3) and has been observed many times. The presence in the respiratory passages of mucus or gastric contents from emesis frequently causes obstruction. Likewise does the relaxation of lingual and pharyngeal musculature, because of large doses of analgesic drugs or anesthetic agents, cause respiratory obstruction and maternal anoxia. Correction of the obstruction and the addition of oxygen under these circumstances will usually quickly restore the fetal heart rate to normal.

Drug anoxia as described by Schreiber³³ included drug toxicity and sensitivity. Alveolar oxygen concentration can be reduced by drugs as has been shown by Waters and his associates.³⁰ They describe actual minute volume respiration reduction as observed after administration of opiates and barbiturates, due to their respiratory depression. This effect is reflected in fetal heart rate, a study which is as yet under investigation.

Stagnant anoxia due to failing or inefficient circulation, a situation occurring in cardiac conditions, was demonstrated by Case 1 (Fig. 1). Anemic anoxia was not active in these cases, yet it can be a potent factor in cases of hemorrhage and shock. The histotoxic factor is still poorly understood.

2. *Failure of Fetus to Receive Oxygen.*—Assuming that the maternal blood stream is well saturated with oxygen, many factors prevent the fetus from obtaining it.

a. *Disturbances of Placental Circulation:* This may be due to excessively long or frequent contractions. Notably anoxia is known to follow tetanic or long-sustained contractions due to the use of oxytocics. Disturbance of circulation by premature separation of the placenta and placenta previa are common. Richardson³⁴ describes first an acceleration and later a slowing of the fetal heart rate in premature separation of the placenta due to a disturbance of the oxygen carbon-dioxide balance, believing that over one-half separation causes a slowing and over three-fourths separation gives a rate of 70 to 90 and frequently causes death. Clifford³⁵ studied the amount of intrauterine asphyxia following placenta previa and found it to be so great that 11 infants died after delivery, due to cerebral changes inflicted by the oxygen want before delivery. He did not note any changes in fetal heart rate.

b. *Cord Entanglement and Prolapse:* These constitute the most frequent causes of intrauterine asphyxia as quoted by the Bureau of

FURTHER STUDIES ON HORMONE EXCRETION DURING THE MENSTRUAL CYCLE*

FRED E. D'AMOUR, PH.D., DENVER, COLO.

(From the Biologic Research Laboratory of the University of Denver)

INFORMATION concerning the daily hormone excretion of the normal human female is valuable for several reasons. Such knowledge contributes to our understanding of the endocrine control of reproductive processes. Before abnormalities can be diagnosed and logical endocrine therapy be instituted, normal values must first be established. The determination of the time of ovulation is a matter of practical importance to many, and the method of urine assays is a promising one in this connection. This paper, which presents the results obtained from the daily assay of urine from 29 cycles, of 5 subjects, for both estrin and gonadotropin, is submitted as a contribution to the slowly accumulating mass of knowledge concerning these problems. It is recognized that much more information, from many sources, must be secured and synthesized before secure conclusions can be drawn.

EXPERIMENTAL

At a recent Federation meeting Dr. Pineus pointed out that much research fails to realize its maximum value because workers have used variations in technique which make direct comparison of results impossible. This criticism is especially valid in such studies as the present one, where the problem's final solution must come from work done by many people. For this reason, and because the methods used have been satisfactory, they are described in some detail.

A. Methods.—Complete twenty-four-hour specimens were collected, chloroform being used as preservative. After filtering, acetic acid was added to a pH of 4.5. Twenty cubic centimeters of a freshly prepared 10 per cent tannic acid solution was added per liter of urine, the mixture was well shaken and permitted to stand overnight in the refrigerator. The precipitate was removed by centrifuging, washed once with 95 per cent alcohol and 4 times with 80 per cent alcohol, centrifuging each time, and finally washed on filter paper with acetone. The precipitate was dried and assayed for gonadotropin. This is essentially the method of Levin and Tyndale.¹

The alcohol and acetone washings, as well as any excess chloroform used as preservative, were evaporated to dryness and the residue returned to the day's urine from which it came. This urine was hydrolyzed for two hours with hydrochloric acid (100 c.c. con. HCl per liter urine), cooled, and extracted with chloroform. The latter was added to corn oil, boiled off, and the corn oil assayed for estrin.

For the assay of gonadotropin, female rats twenty-six days old at the time of first injection were used. The precipitate was ground in saline so that the total dose to be given each rat was present in 1.5 c.c. Injections were made once daily for three days (0.5 c.c. per injection) and the animals sacrificed at the end of one hundred hours. The uteri were carefully dissected, pressed between moist filter paper and weighed. Except where otherwise noted, the dose administered in this study was the equivalent of three hours' urine excretion per rat. This permitted

*This investigation was supported, in part, by a grant from the Penrose Fund of the American Philosophical Society.

determined by continuous or at least very frequent auscultation of the fetal heart sounds. Institution of specific therapy, oxygen, at this time will in many cases either partially or completely restore the fetal heart rate to normal and successfully combat the anoxia. The response to oxygen therapy should be noted within ten minutes and frequently is apparent in less than five minutes. If after fifteen minutes of therapy no improvement is noted, it may be assumed that oxygen will be of no value. The time of preparation of a patient for operative delivery is usually more than ten minutes and this can be carried out while the oxygen is being given; thus no hazard is created for the infant. Frequently the improvement in the fetal heart rate will obviate the necessity of exigent operative delivery and its danger to mother and infant.

CONCLUSIONS

1. Impending fetal asphyxia can be determined by careful frequent auscultation during active labor.
2. A method for continuous auscultation and recording of fetal heart sounds is described.
3. Fetal heart arrhythmia due to anoxia is described and the response to oxygen recorded.
4. The etiologic factors of fetal anoxia are discussed.
5. Early recognition of fetal anoxia and treatment by maternal oxygen therapy will prevent many cases of asphyxia neonatorum.

REFERENCES

- (1) *Mayor, F. I.*: Bibliotheque, Universelle de Geneva, 1818. (2) *Fasbender, H.*: Geschichte de Geburtshülfe, Jena, 1906, Gustav Fischer, p. 431. (3) *Lejumeau de Kergaradec, N. J. A.*: Memoire sur l'auscultation applique à l'étude de la Grossesse, Paris, 1822. (4) *Kennedy, Evory*: Observations on Obstetric Auscultation, New York, 1843. (5) *Naegle, H. F.*: Die Geburtshülffliche Auskultation, Mainz, 1838. (6) *Hohl*: Die Geburtshülffliche Auskultation, 1833. (7) *Cummings, James*: The Uterine Souffle and the Fetal Heart, Edinburgh, 1875. (8) *Von Winckel, F.*: Handb. der Geburtshülfe, 1903. (9) *Reed, Charles*: Surg. Gynec. & Obst. 24: 545, 1918. (10) *Sachs, E.*: Ztschr. f. Geburtsh. u. Gynäk. 82: 284, 1920. (11) *Frey, E.*: Ibid. 88: 261, 1924. (12) *Bartholomew, R. A.*: AM. J. OBST. & GYNEC. 10: 89, 1925. (13) *Freed, Frederick*: Ibid. 14: 659, 1927. (14) *Hofbauer, J., and Weiss, O.*: Zentralbl. f. Gynäk. 32: 429, 1908. (15) *Smith, Arthur L., and Hervert, W. J.*: AM. J. OBST. & GYNEC. 40: 102, 1940. (16) *Leff, M.*: Ibid. 20: 108, 1930. (17) *Davis, C. H.*: Ibid. 14: 806, 1927. (18) *Danforth, W. C., and Davis, C. H.*: J. A. M. A. 81: 1090, 1923. (19) *Danforth, W. C.*: AM. J. OBST. 76: 563, 1917. (20) *Ferguson, R.*: AM. J. Surg. 31: 103, 1917. (21) *Waters, Ralph M., and Harris, John W.*: Anesth. & Analg. 10: 59, 1931. (22) *Schmidt, Carl F.*: AM. J. Physiol. 84: 202, 1928. (23) *Yant, W. P., Chorymak, John, Schrenk, H. H., Patty, F. A., and Sayers, R. R.*: Pub. Health. Bull., p. 211, 1934. (24) *Courville, C. B.*: Medicine 15: 129, 1936. (25) *Schreiber, Fredrick*: J. A. M. A. 111: 1263, 1938. (26) *Snyder, Franklin, and Rosenfeld, Morris*: AM. J. Physiol. 119: 153, 1937. (27) *Rech, W.*: Arch. f. Gynäk. 147: 82, 1931. (28) *Leake, D. C., Leake, E. W., and Koehler, A. E.*: J. Biol. Chem. 56: 319, 1923. (29) *Ronzoni, E., Koechig, I., and Eton, E. P.*: Ibid. 61: 465, 1924. (30) *Waters, Ralph M., Wineland, A. J., and SeEVERS, M. H.*: Anesth. & Analg. 10: 10, 1931. (31) *Eastman, Nicholson, J.*: AM. J. OBST. & GYNEC. 31: 563, 1936. (32) *Smith, Clement, A.*: Surg. Gynec. Obst. 69: 584, 1939. (33) *Schreiber, Frederick, and Gates, Nathaniel*: J. Michigan State M. Soc. 37: 145, 1938. (34) *Richardson, Garwood C.*: AM. J. OBST. & GYNEC. 32: 429, 1936. (35) *Clifford, Stewart H.*: Ibid. 39: 388, 1940. (36) *Barcroft, J.*: Physiol. Rev. 16: 103, 1936.

pituitary relationship based on animal experimentation. It should be added that menstrual cycles over the succeeding two years have been normal; therefore the bleeding noted could not have been related to the onset of the menopause.

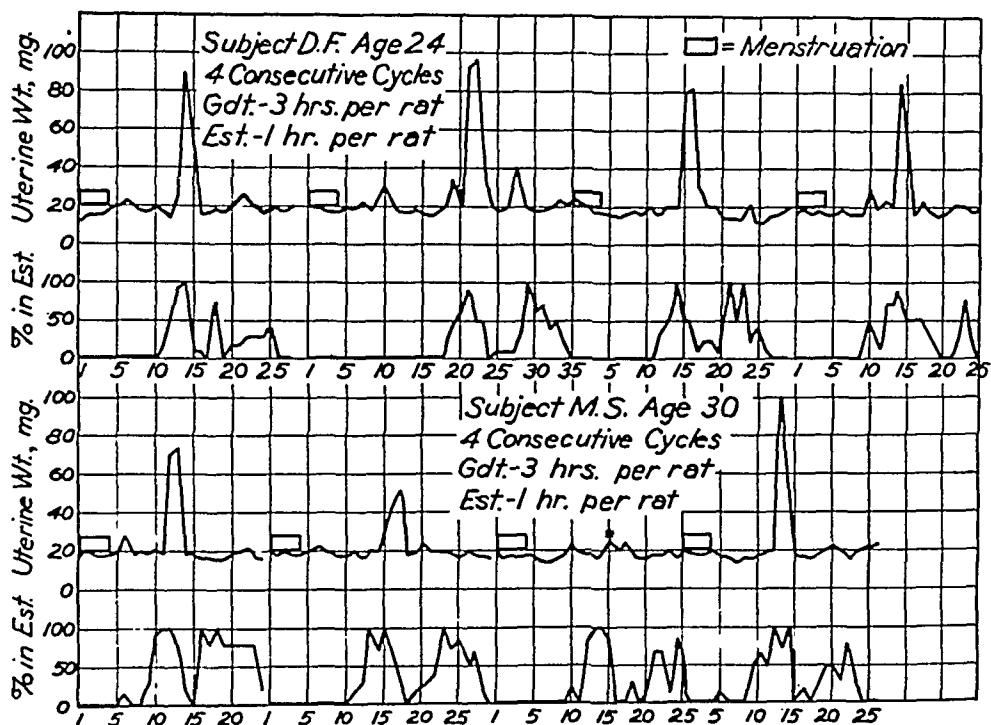


Chart 2.

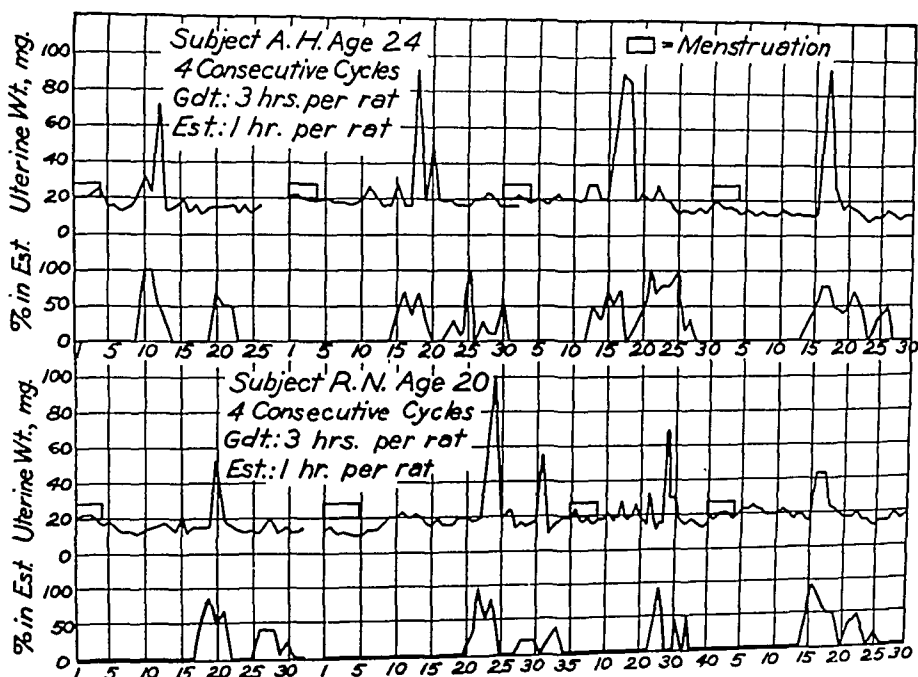


Chart 3.

In the upper half of Chart 2, four cycles of Subject D. F. are illustrated and in the lower half, the same number for Subject M. S. Both are single women with normal gynecologic histories. The third cycle of M. S. is presumably anovulatory, the others normal.

the use of 8 rats per day's urine, which, while perhaps still not enough to justify use of the word "assay," is at least a great improvement in sensitivity over the ovarian weight method. There is no correlation between volume of urine, nor weight of precipitate, and activity; it is therefore necessary to base results on "hours of excretion." No difficulty whatever was experienced with toxicity of precipitates; of the thousands of animals used in this study not one died as the result of injection.

In the assay of estrin, the chloroform was placed in such volume of corn oil that 0.5 c.c. contained the required dose. Except where noted, the curves are based on a dose of one hour's urine excretion per rat. This permits the use of 24 animals per day's sample, sufficient for reasonable accuracy of results. The test is the well-known vaginal method of Allen and Doisy. The sensitivity of the colony was frequently checked with International Standard estrone.

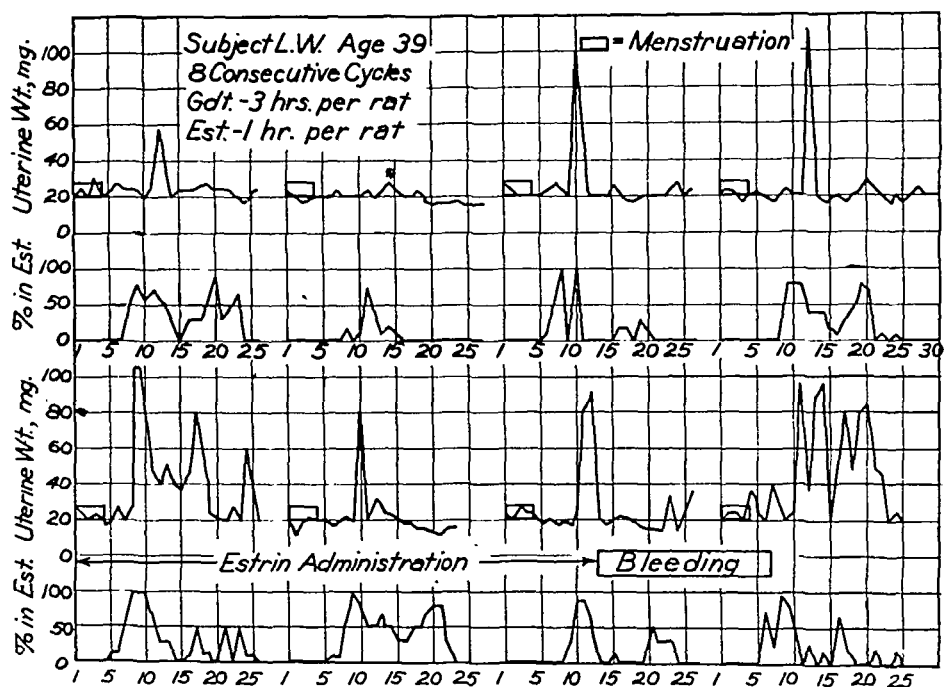


Chart 1.

B. Results.—These are presented in Charts 1 to 4. Each chart includes 8 cycles, 4 in the upper half and 4 in the lower, the upper line of each half representing the gonadotropic assay in terms of average uterine weight, and the lower, the estrin assay for the same cycle, in terms of percentage of animals showing a positive response.

The subject (Chart 1), L. W., aged 39 years, married, mother of 3 children, had a normal gynecologic history. The first four cycles were normal, considering the second, possibly anovulatory, as normal. (The question of anovulatory cycles is discussed below.) During the last four cycles she subjected herself to estrin administration. This experience will be more fully described elsewhere but a few points may be noted here. During the first of these cycles the gonadotropic output was increased, which was perhaps to be expected on the basis of a primary stimulating effect of estrin upon the pituitary. The second and third cycles were normal; since the dosage of estrin was small (only 0.04 mg. estradiol daily), no demonstrable inhibition of the pituitary was produced. However, an alarming episode of bleeding occurred, as noted on the graph, and the administration of estrin was discontinued. The apparent excessive activity of the pituitary during the fourth cycle may be explained as a release from a certain degree of pituitary inhibition. These explanations are, of course, speculative, but are in line with theories of ovary-

TABLE I

SUBJECT	TOTAL CYCLES	POSITIVE CYCLES	DAYS PRECEDING MENS. OF GONADOTROPIN PEAK	PRESUMABLY ANOVULATORY
L. W.	8	7	13-15-16-16-14-15-14	1
D. F.	4	4	13-14-14-14	0
M. S.	4	3	12-13-13	1
A. H.	6	5	13-15-15-15-16	1
R. N.	7	6	13-12-14-14-12-12	1
	29	25	Min. 12; Max. 16; Av. 15.1	4

In a previous study² I reported a series of 50 cycles in which the daily gonadotropic output was tested. In that study the criterion of activity was increase in weight of the rat's ovaries. In many cases more than one gonadotropic peak occurred during a given cycle. In the present study, excluding L. W.'s cycles influenced by estrin administration, this irregularity was not present. No doubt the explanation lies in the greater sensitivity of the uterine weight method, which permits the use of a smaller dosage and a larger number of animals. If, as seems likely, the pituitary maintains some degree of gonad-maintaining activity throughout sexual life, the problem becomes one of determining peaks in its secretory activity. For this, the injection of large amounts of material into a few animals is unsatisfactory. On the basis of the present data, there is no evidence for multiple ovulation. The final answer to this, as to many related questions, must await further study.

There remains the question of interpretation of those cycles in which no gonadotropic peak occurs. In the paper mentioned, 3 of the 50 cycles were of this character; in this study, 4 of 29. If the sudden output of a relatively large amount of gonadotropin indicates the operation of a mechanism resulting in ovulation, then its absence should mean the failure of ovulation to occur and these cycles may be considered anovulatory. An interesting, probably meaningless, point is that six of the seven cycles of this character occurred in the spring.

Summarizing, it may be said that with the method and dosage used, a considerable degree of uniformity in results was obtained, in that 25 of 29 cycles gave positive responses between twelve and sixteen days preceding menstruation; the other four no reaction, being presumably anovulatory. Further, that the use of a more sensitive method and larger numbers of animals has eliminated the frequent occurrence of multiple peaks in gonadotropin output previously noted. Finally, that, in my opinion, the urinary assay method, with due regard to details of dosage and technique, is a valuable one, but that much further data must be obtained before its reliability will have been sufficiently established to warrant secure conclusions, from it alone, as to the time of ovulation.

B. Levels of Hormone Excretion and Time Relationship.—In the preceding paragraphs the gonadotropic output was considered. As a test for ovulation time, a dosage of three hours' urinary excretion per rat appears satisfactory. The uterine reaction obtained is equivalent to that given by 0.5 to 1.0 international units of either chorionic or pregnant mare's serum gonadotropin. The total excretion per peak therefore equals from 4 to 16 I. U. The question arises as to the secretory

The upper half of Chart 3 is devoted to Subject A. H. and the lower half to Subject R. N. Their cycles are continued on Chart 4, there being 6 consecutive cycles for the first subject and 7 for the second. Both are single young women with normal histories. Each shows one presumably anovulatory cycle, the rest being normal.

Chart 4 shows the results found when the last cycle of A. H. and the last two of R. N. were repeated, the dose of each hormone being doubled. The original graphs are re-drawn with the results on double dosage indicated by the broken lines.

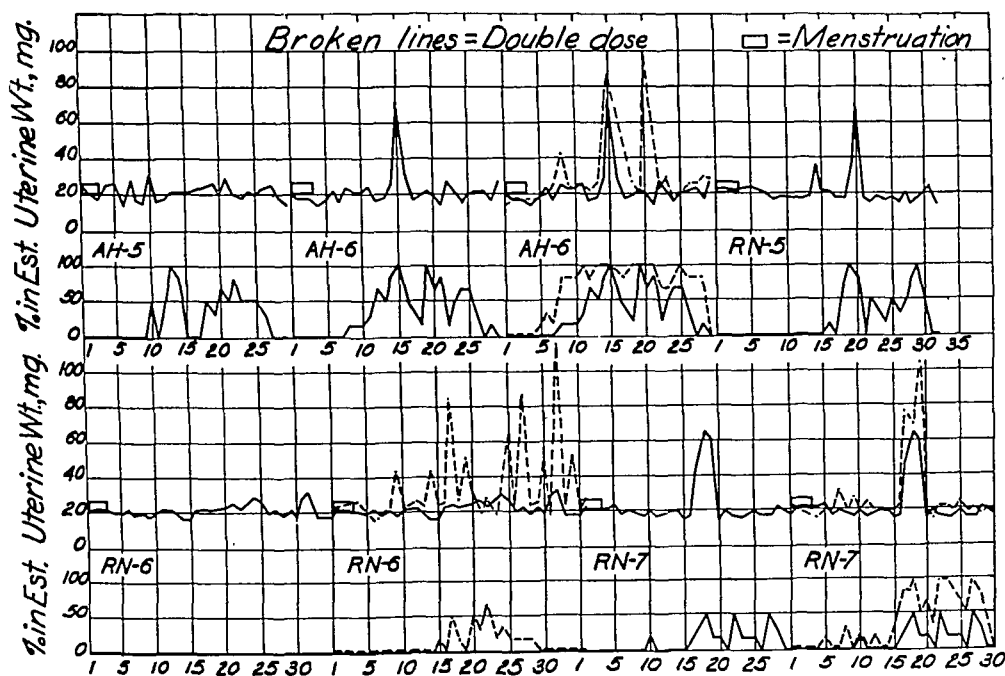


Chart 4.

DISCUSSION

A. Time of Ovulation.—It is unnecessary to review here the extensive literature on this subject. Suffice it to say that evidence from all sources is in general agreement that this event occurs some ten to sixteen days prior to the onset of the next menstruation. Here we are concerned primarily with the question of the practicability of the urine assay method, which, although tedious, has the advantage of making small demands upon the subject and is therefore useful for long-time studies. It is, of course, an indirect method and, as is true of all indirect methods, such as uterine motility, vaginal smear, etc., there is no certainty of the relation of the observed phenomenon to ovulation. The only test for the validity of any such method therefore is its comparison with results achieved with others. That the agreement is good is indicated by Table I.

It happens that Subject L. W. has relatively short cycles, averaging 26 days, while those of R. N. average 34 days (one of 42 days), yet the peak occurs approximately the same number of days before the ensuing menses in both cases. This supports the view held by most workers that the luteal phase of the cycle is of relatively fixed duration.

that the first effect of estrin upon the pituitary is to stimulate it to secrete (or release) gonadotropin. Briefly, the mechanism of ovulation may then be postulated as follows: The pituitary maintains the growth and development of the ovary continuously. This is evidenced by the effects of hypophysectomy primarily, plus the slight additional verification presented in the described assay for gonadotropin at high dosage levels. With the ripening of the follicle, the secretion of estrin begins, probably as early as the seventh day, increasing in amount until it builds up to a peak. This increasing concentration acts as a stimulus to the pituitary whose increased output is demonstrated by the appearance of the gonadotropin peak. That this gonadotropin is pituitary in origin seems likely⁴ but whether it differs only in amount or perhaps qualitatively as well from the ovary-maintaining principle is not known. It is believed⁵ that a proper combination of both follicle-stimulating and luteinizing hormones is necessary for ovulation; that addition of luteinizing hormones to follicle-stimulating hormone preparations gives an augmented ovarian reaction in the immature rat⁶; and there is evidence that the chief effect of estrin stimulation on the pituitary is, at first, to increase the output of luteinizing hormone.⁷

The second wave of estrin secretion, usually as great as or greater in amount than the first, does not usually result in a rise in gonadotropin. This estrin is presumably secreted by the corpus luteum and its inability to stimulate the pituitary must be due to the inhibiting effect of the progesterin being produced simultaneously. To check this point, as well as to render the picture complete in other respects, simultaneous determination of progesterin (pregnanediol) is necessary. We have attempted to do this by the method of Venning⁸ but although satisfactory for pregnancy urine, we have not been able to convince ourselves of the reliability of this method as applied to daily samples of normal urine.

There remain to be considered the few cycles which do not fit into the theory suggested above. In the second cycle of L. W. (Chart 1), it appears that the estrin output, although apparently normal, did not result in sufficient hypophyseal stimulation to produce a peak. From the failure of a second estrin wave to appear, one might assume that ovulation had not occurred. Cycle R. N.-6 shows an apparent failure of estrin secretion, consequently no hypophyseal activity and no ovulation. Cycles M. S.-3 and A. H.-6 are anomalous and cannot be explained, as in both cases a second wave of estrin (presumably from the corpus luteum) occurred without the hypophyseal activity assumed to be necessary for ovulation. These occasional aberrant cycles cannot fail to cast doubt both on the validity of the theory and the reliability of the method. I can only repeat that, for the establishment of either, the accumulation of more data is an absolute necessity.

SUMMARY

Day-by-day assays, for both estrin and gonadotropin, during a total of 29 cycles, of 5 subjects, have been made. The results were as follows:

1. As regards time of ovulation: Of the 29 cycles, 25 gave evidence of ovulation occurring between the twelfth and sixteenth days preceding the onset of the next menstruation; the other 4 were considered anovulatory.

activity of the pituitary at other times during the cycle. The difficulty in determining this is that the amount of gonadotropin in each day's output is so small that with present methods it is impossible to assay it at two or three dosage levels, using a sufficiently large number of animals on each dose for the results to be meaningful. We did repeat three cycles, A. H.-6 and R. N.-6 and 7 (see Chart 4), on double the original dose, i.e., six hours' excretion per rat instead of three. Half the urine having been used on the original dose, only 2 rats could be used on the larger, and the results cannot be considered quantitative. For A. H.-6 the double dose curve shows two additional peaks, R. N.-6 a saw-tooth effect with many positive responses and R. N.-7 a duplicate of the original curve. While no conclusion as to amount or regularity of secretion is possible, activity of the pituitary, as indicated by the appearance of its secretion in the urine, does occur at other times than the mid-interval.

The excretion of estrin during the menstrual cycle has been investigated by a number of workers, Gustavson and others³ having contributed probably the most thorough study. They found two peaks in estrin excretion as typical of the normal cycle, the amount at the peaks being equivalent to 600 to 800 I. U. In the present study a somewhat simpler method, both of preparing the sample and indicating the results was used, the results being shown simply on the basis of the percentage of animals responding positively to a dose (as a rule) of one hour's excretion per rat. Exact quantitative comparison is not possible but peaks showing 100 per cent positive responses are equivalent to an output of approximately 800 I. U. The possibility of estrin excretion at a lower level during phases of the cycle other than the normal waves was considered and in the three duplicate cycles shown in Chart 4 the assay was repeated using a dose of two hours' urine per rat. As before, fewer animals (6 only) could be used on each day's sample. For A. H.-6 the excretion on the higher dose was found to be almost continuous after the first week. For R. N.-6 (a peculiar cycle in that no indication of estrin excretion was found at the usual dose) the higher dose showed that estrin was being excreted, although at a low level, for R. N.-7 the curves parallel each other.

Summarizing the data concerned with estrin excretion, a two-wave type of curve appears to be normal although the waves themselves are irregular in outline; at the peak some 600 to 800 I. U. are excreted daily; assay at high dosage shows estrin may be excreted throughout the cycle except for the first week.

A comparison of the time of occurrence of corresponding estrin and gonadotropin peaks leads to the interesting finding that the excretion of estrin invariably precedes that of gonadotropin. Presumably the same is true of their production by the glands involved, and, if this finding is verified, the somewhat unexpected conclusion must be reached that the original stimulation to ovulation is ovarian rather than hypophyseal in origin. While at variance with the commonly accepted view that the pituitary is the motor governing ovarian function, this finding is supported by the results of animal experimentation, which indicate

the relatively few babies found to be syphilitic in the pediatric follow-up clinic. This impression becomes even more significant when one takes into account the incidence of patients seen late in pregnancy and the number in whom irregular and inadequate therapy had been instituted.

Much has been written recently concerning the reaction of the pregnant woman to the arsenicals^{9, 12, 13} and of the beneficial effect of pregnancy on the syphilitic state.¹⁴ Very little is known concerning the effect of these drugs on the fetus in utero although some believe that antisyphilitic therapy probably does carry a mortality rate for the fetus.

Because of the occasional occurrence of definitely syphilitic babies from mothers showing no clinical signs of the disease and whose serology is negative, many obstetricians have adopted the rule of treating every patient during pregnancy whose serology is suggestive or whose history or that of her husband gives positive evidence of this disease or of treatment for it.¹¹ It seems obvious that such rules bring under this regimen those patients who have been thoroughly treated and biologically cured of syphilis as well as a few patients who have never had the disease.

The records of the patients who have been treated in this Hospital for the past seven years have been examined in an effort to obtain a clearer view of the factors which play a part in the satisfactory outcome of the fetus; to determine, if possible, which patients may expect a satisfactory outcome of the pregnancy; and to attempt to find whether type and amount of antisyphilitic therapy as such appreciably affect the fetal mortality and incidence of infection.

MATERIALS AND METHODS

The charts of 386 patients in whom 453 pregnancies had occurred were reviewed. One hundred ninety-two of these pregnant women had been delivered on the in-patient service of the New York Lying-in Hospital and 261 had been cared for on the out-patient service of this hospital at the John E. Berwind Free Maternity Clinic of New York City.

All of these patients had had pregnancies occurring between the years 1932 and 1939, inclusive, and had been registered in these services. All had received routine antenatal care in addition to the antisyphilitic therapy, and each patient had been given more than one treatment for the suspected syphilis.

The scale of society from which these people came ranged from the very poor, most of which were Berwind Out-door Clinic patients, to the middle stratum of society seen in the New York Hospital. Two hundred and thirty-nine of these pregnancies were in colored and 214 in white women.

Upon registration the prospective mothers had been subjected to a thorough medical history and a complete physical examination. Laboratory work on all patients consisted of a serologic test for syphilis (Wassermann or Kline) and a hemoglobin determination of the blood; albumin and sugar were tested for in the urine.

Following the finding of a history of syphilis, a history of treatment, or positive or questionable serology, the patient was immediately referred to the syphilitic clinic where a more complete venereal history was obtained and the serology repeated with specimens being sent to the Laboratories of the Board of Health of the City of New York. In doubtful cases the families of the patients were investigated. All patients were treated during the pregnancy who had histories of syphilitic infection, who had been treated previously for this disease, or whose serology and family investigation failed to leave any reasonable doubt that the patient might have syphilis.

2. As regards hormone excretion levels: The amount of gonadotropin produced during peaks of activity was equivalent to from 4 to 16 I. U. Some evidence was obtained supporting the view of hypophyseal activity at other times than the mid-interval. The excretion of estrin took place in two waves, the daily output at the peak being approximately 800 I. U. Some degree of estrin excretion may take place at other times during the cycle except during the first week.

3. As regards time relationship of hormone excretion: Invariably the ovarian activity, as indicated by increasing estrin excretion, precedes hypophyseal activity, as indicated by the gonadotropin peak. On the basis of this finding a theory of the mechanism controlling ovulation is tentatively suggested.

REFERENCES

- (1) *Levin, L., and Tyndale, H. H.*: Proc. Soc. Exper. Biol. & Med. 34: 516, 1936. (2) *D'Amour, F. E., Funk, D., and Liverman, H.*: AM. J. OBST. & GYNEC. 37: 940, 1939. (3) *Gustavson, R. G., Mason, L. W., Hays, E. E., Wood, T. R., and D'Amour, F. E.*: Ibid. 35: 115, 1938. (4) *D'Amour, F. E.*: Am. J. Physiol. 127: 649, 1939. (5) *Van Dyke, H. B.*: The Physiology and Pharmacology of the Pituitary Body, Chicago, 1939, The University of Chicago Press 2: p. 220. (6) *Fevold, H. L.*: Cold Spring Harbor Symposia on Quantitative Biology 5: 94, 1937, The Biological Laboratory, Cold Spring Harbor, L. I., N. Y. (7) *Fevold, H. L., Hisaw, F. L., and Greep, R. O.*: Am. J. Physiol. 114: 508, 1937. (8) *Fenning, E. H.*: J. Biol. Chem. 126: 595, 1938.

AN EVALUATION OF THE EFFECT OF ANTENATAL ANTISYPHILITIC THERAPY ON FETAL MORTALITY AND ON CONGENITAL SYPHILIS

L. V. DILL, M.D., H. J. STANDER, M.D., AND C. E. ISENHOUR, M.A.,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College, and the New York Hospital)

ONE of the greatest steps forward in the history of obstetrics was the advent of the treatment of syphilis in the pregnant woman,¹ with the coincident reduction of fetal death rate and incidence of fetal infection. Prior to this time not only one-half of the fetuses of these women were born dead but also only a small number of those both dead and living were found to be unaffected by the virus.²⁻⁵ With institution of adequate treatment the reduction of this astounding devastation of fetal life has been almost miraculous, and striking results have been obtained even with scanty amounts of therapy.⁶⁻⁹

There is no room for doubt that adequate antisyphilitic therapy instituted early in the course of pregnancy will greatly reduce the number of disastrous and infected products of conception, and studies have shown that therapy prior to conception, even inadequate, materially affects the incidence of infection in the fetus.^{8, 10, 11}

Although we have seen a comparatively large number of pregnant women with positive serology, we have been impressed with the scarcity of signs and symptoms of congenital syphilis in the fetuses and with

York Hospital or rarely to one of the New York City hospitals. No patients are included in this series who were not delivered at Berwind or in the New York Hospital, although a few of the Berwind cases were lost to City Hospitals because of complications. In this sense the New York Hospital series and the Berwind series are complementary rather than comparable.

CONTROLS

Four hundred and fourteen patients who had 500 pregnancies, 200 pregnancies from the New York Hospital and 300 from the Berwind Clinic, were used as controls for the syphilitic series. Approximately an equal number of consecutive deliveries were taken from each of the years included in the syphilitic group. These patients were taken care of in the same manner as the syphilitic group, but at no time showed evidence of even doubtful serology and had no history of syphilitic infection or treatment for this disease. An effort was made to approximate the parity and the age of the patients in the syphilitic group (Table I). It is to be noted, however, that the percentage of colored patients in the control group is considerably lower than the percentage in the syphilitic series. No follow-up observations on these babies are available and no Wassermann test or long bone studies were made, except of stillborn babies.

No effort was made to collect a series of untreated syphilitic patients, as the paucity of the material would make these figures statistically unsound.

TABLE I. COMPARATIVE DATA ON THE OBSTETRIC TYPE OF PATIENT INCLUDED IN THIS SERIES

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of patients	175	211	142	272
Race {White	115	81	128	171
{Colored	60	130	14	101
Average age	27.7	29.5	27.3	28.8
Number of previous pregnancies	349	831	238	876
Average per patient	1.9	3.8	1.6	3.2
Number of pregnancies observed	192	261	200	300
Babies followed	149	73	---	---
*Maternal {Positive	142 (74%)	----	---	---
serology {Negative	50 (26%)	----	---	---
†Maternal {Positive	121 (63%)	198 (76%)	0 (0%)	0 (0%)
Wassermann {Negative	71 (37%)	63 (24%)	200 (100%)	300 (100%)

*Both Wassermann and Kline tests were done on N. Y. Hospital patients.

†Only the Wassermann test was done on the Berwind group.

OUTCOME OF PREVIOUS PREGNANCIES

The 386 patients of our syphilitic series had had 1160 previous pregnancies, almost two each for the New York Hospital group and four each for the Berwind group (Table II). Although the Berwind group showed slightly more living term pregnancies than the New York Hospital group, more than two-thirds of these pregnancies in each group had ended in term deliveries and had resulted in living children, which at this time are living and clinically well or have succumbed to one of the usual childhood diseases, according to the maternal history. The nonsyphilitic controls show a similar group difference although a distinctly higher percentage of term living fetuses is noted.

The greatest loss of life in both syphilitic and control group occurred in the early abortion division, with a noticeably higher incidence in the New York Hospital series.

The treatment at the in-patient department has consisted for the most part of continuous therapy with arsphenamine alternated with courses of bismuth. Some of the patients have received neoarsphenamine and bismuth in alternating courses and some have received them in combined therapy. Recently combined therapy with mapharsen and bismuth has been instituted. A few patients have had indications for the use of tryparsamide or silver arsphenamine, but these have been infrequent. At the Berwind Clinic all therapy consisted of neoarsphenamine, alternated with courses of bismuth.

At the time of delivery, the maternal and cord Wassermanns were done, and the placenta examined grossly and microscopically. The blood Wassermann reaction of the baby and x-rays of the long bones were done six to nine days post partum.

Autopsies were obtained on all but a few of the dead babies and spirochetes were routinely searched for in most of these bodies. A culture of the heart blood was usually done.

All living babies were routinely referred to the pediatrics department of the hospital for follow-up observations and were seen at three-month intervals or more frequently if conditions warranted. The babies from the Berwind Clinic were referred usually to this clinic or to the nearest City health center. Routine serologic tests, x-ray studies of the long bones, and careful physical examinations were made at regular intervals. An attempt was made to follow all babies for eighteen months if proved to be not infected, and for a longer period if syphilitic.

The charts of these patients were studied from the points of view of the age, race, and outcome of the previous pregnancies. The blood Wassermanns on admission, at delivery, and at six weeks and two years post partum were recorded as well as the duration of antenatal care and duration of the pregnancy. The labor was studied with reference to duration, type of pelvis, and complications of the normal mechanism in order to rule out obstetric trauma as a cause of death or poor condition of the baby. The baby was studied as to condition at birth, length, weight, x-ray of long bones, cord Wassermann, placental weight and pathology. The condition of the baby and the blood Wassermann at six weeks and at the end of the pediatric follow-up were also considered.

The previous course of the mother, when known, with reference to the serology, duration of the disease, and exact amount of previous treatment, was recorded. (Records from the source of treatment were consulted when possible; otherwise the history of the patient was taken as the source.)

The treatment during the present pregnancy was recorded as to duration, amount and type, and severe treatment reactions were noted. The course following delivery at the end of six weeks and two years with the serology and type of treatment was included.

In the classification of babies of the series observed, babies were considered "term" which were above 2,500 Gm. in weight or above 45 cm. in length. Babies were considered premature which weighed from 1,500 to 2,500 Gm. or were below 45 cm. in length. All products of conception from 100 to 1,500 Gm. were considered "late abortions" and those below 100 Gm. were considered "early abortions."

The classification of babies of the previous pregnancies was carried out as follows: Babies were considered "term" which were above 5 pounds or later than eight months; babies were considered premature which were above 3 pounds or later than seven months' gestation; when delivery occurred between the fourth and sixth months the product was considered to be a "late abortion" and when prior to the fourth month was considered an "early abortion."

Babies were classified as normal only after numerous physical examinations, blood serologies and x-rays of the long bones over a period of six months or more had failed to reveal evidence of the disease. No babies were classified as syphilitic by autopsy since none were found to have spirochete-containing tissue.

Under the classification of abortions no pregnancies terminated by induction or operative interference were included in this series, either in the previous or the present pregnancies.

The two groups are not quite comparable in that any serious complication of the antenatal course or delivery encountered at Berwind Clinic is referred to the New

to treatment before the end of the first month of life, had an immediate reversal of serology. Therapy was discontinued after a few months and long follow-up failed to reveal return of the positive serology or clinical evidence of syphilis; therefore these babies were considered normal.

It is obvious that the percentage of syphilitic babies is higher in the group where the maternal Wassermann was positive, but we were unable to find any significant difference in the number of fetal casualties.

It is of interest to note that we found 4 infants in whom the blood Wassermann failed to become negative even after two or three months, and in one case it remained positive for six months. These children have shown no clinical evidence of syphilis and with no treatment have remained clinically and serologically free from the disease for more than four years.

TABLE IV. SHOWING THE INCIDENCE OF SIGNIFICANT CHANGES IN THE PLACENTA AND THE LONG BONES OF THE INFANT AND OF A POSITIVE REACTION OF THE CORD BLOOD AND OF THE MOTHER'S BLOOD TO THE STATUS OF THE FETUS

	SYPHILITIC BABIES		NONSYPHILITIC BABIES	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of babies followed	9	0	131	68
Cord Wassermann { Negative	1 (11%)	0 (0.0%)	86 (81%)	49 (83%)
{ Positive	8 (89%)	0 (0.0%)	20 (19%)	10 (17%)
Placenta { Negative	8 (100%)	0 (0.0%)	97 (98%)	40 (91%)
{ Positive	0 (0.0%)	0 (0.0%)	2 (2%)	4 (9%)
Long bones { Negative	7 (78%)	0 (0.0%)	81 (96%)	42 (98%)
{ Positive	2 (22%)	0 (0.0%)	3 (4%)	1 (2%)
Maternal Wassermann { Negative	1 (11%)	0 (0.0%)	50 (38%)	14 (21%)
{ Positive	8 (89%)	0 (0.0%)	81 (72%)	54 (79%)

We were surprised to find that roentgenograms of the long bones were frequently in error in the diagnosis of congenital syphilis on the appearance of the irregularities of the bone metaphysis. Approximately 95 per cent of the x-rays of the long bones were negative for syphilis when the baby was normal, but 2 to 4 per cent of these babies also showed the changes which were diagnosed as definitely syphilitic by McLean's criteria.¹⁵⁻¹⁷ Of the syphilitic babies, 20 per cent were found to have bone changes compatible with congenital syphilis, but in 80 per cent the bones were considered negative for significant x-ray changes (Table IV).

Placental findings were also of note in that 90 to 95 per cent of the placentas from the nonsyphilitic children were classified as normal, while 2 to 4 per cent of these babies had placentas which were classified as syphilitic according to the changes described by Frankel.¹⁸ In the syphilitic group, none of the placentas showed histologic evidence of syphilis.

Of the cord Wassermans done on 6 of the syphilitic babies, only one was found to be negative, and here the Kline test was strongly positive. The cord Wassermann was positive in 16 to 18 per cent of the normal babies and negative in 80 to 85 per cent. We found only one positive cord Wassermann in a mother whose blood Wassermann was reported repeatedly negative and this baby was definitely syphilitic. It is worthy of note, however, that the Kline reaction in this patient was strongly positive.

No babies either deadborn or dying in the neonatal period were found to be syphilitic at post-mortem examination, either by the supposedly characteristic changes in the bones or by finding spirochetes in the tissues.

The placental weights and the weights of the babies of syphilitic mothers of both groups were compared with those of the control groups (Table V). The Berwind babies averaged about 100 Gm. more than those of the New York Hospital group, and the controls were slightly heavier than the babies of the syphilitic mothers.

The number of term deadbirths and neonatal deaths as well as premature deadbirths and late abortions was significantly higher in the syphilitic groups than in the nonsyphilitic control groups.

TABLE II. SHOWING THE OUTCOME OF PREVIOUS PREGNANCIES IN THE TWO GROUPS OF SYPHILITIC PATIENTS AS COMPARED WITH SIMILAR PREGNANCIES IN ANALOGOUS GROUPS OF NONSYPHILITIC MOTHERS

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of patients	175	211	142	272
Total pregnancies	343	817	238	876
Term { Living	233 (67.9%)	614 (75.2%)	190 (79.8%)	751 (85.7%)
Deadborn	14 (4.1%)	38 (4.7%)	5 (2.1%)	13 (1.5%)
Neonatal	7 (2.0%)	18 (2.2%)	0 (0.0%)	8 (0.9%)
Premature { Living	2 (0.6%)	8 (1.0%)	1 (0.4%)	3 (0.3%)
Deadborn	7 (2.0%)	38 (4.7%)	2 (0.8%)	0 (0.0%)
Neonatal	1 (0.3%)	5 (0.6%)	2 (0.8%)	4 (0.5%)
Abortions { Early	65 (18.9%)	68 (8.3%)	35 (14.7%)	91 (10.4%)
Late	14 (4.1%)	28 (3.4%)	3 (1.3%)	6 (0.7%)

OUTCOME OF PRESENT PREGNANCIES

More than 80 per cent of the pregnancies of syphilitic patients in the New York Hospital group and 90 per cent of the Berwind pregnancies observed terminated in living term babies, a percentage which is significantly lower than the corresponding number occurring in the nonsyphilitic control patients (Table III).

In these pregnancies the greatest loss of life occurred in the term deadbirth and neonatal death groups, this loss exceeding the control figures by more than 100 per cent. Here again there is a considerable preponderance of fetal mortality in the New York Hospital group.

The number of premature living babies and premature neonatal deaths is distinctly increased over control levels only in the New York Hospital cases.

The high incidence of early abortion of the New York Hospital control group is well out of proportion to both syphilitic groups and to that seen in the Berwind nonsyphilitic patients.

TABLE III. SHOWING THE OUTCOME OF PRESENT PREGNANCIES WITH TREATMENT IN SYPHILITIC PATIENTS AS COMPARED WITH SIMILAR PREGNANCIES IN ANALOGOUS GROUPS OF NONSYPHILITIC MOTHERS

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of pregnancies	192	261	200	300
Term { Living	148 (77.1%)	239 (91.6%)	172 (86.0%)	289 (96.3%)
Deadborn	14 (7.3%)	6 (2.3%)	6 (3.0%)	2 (0.7%)
Neonatal	8 (4.2%)	7 (2.7%)	1 (0.5%)	1 (0.3%)
Premature { Living	12 (6.3%)	4 (1.5%)	6 (3.0%)	4 (1.3%)
Deadborn	1 (0.5%)	2 (0.8%)	1 (0.5%)	2 (0.7%)
Neonatal	4 (2.1%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Abortions { Early	2 (1.0%)	1 (0.4%)	10 (5.0%)	0 (0.0%)
Late	3 (1.6%)	1 (0.4%)	4 (2.0%)	2 (0.7%)

EVALUATION OF DIAGNOSTIC CRITERIA FOR CONGENITAL SYPHILIS

With pediatric follow-up of more than 6 months we were able to find only 9 pregnancies resulting in babies which could definitely be called syphilitic, and all of these were subjected to treatment (Table VIII). Two other babies, subjected

percentages of syphilitic babies were noted in the younger age groups, and that the incidence of infected babies dropped off with the ascending age of the patient. This was also found to be true for the percentage of dead babies, with the single exception of those occurring in the "40 years of age" group. We were not, however, able to show that the increased age placed the patient in a safe class for prognosis for the fetus inasmuch as syphilitic babies were observed even in the older age groups (Chart 4).

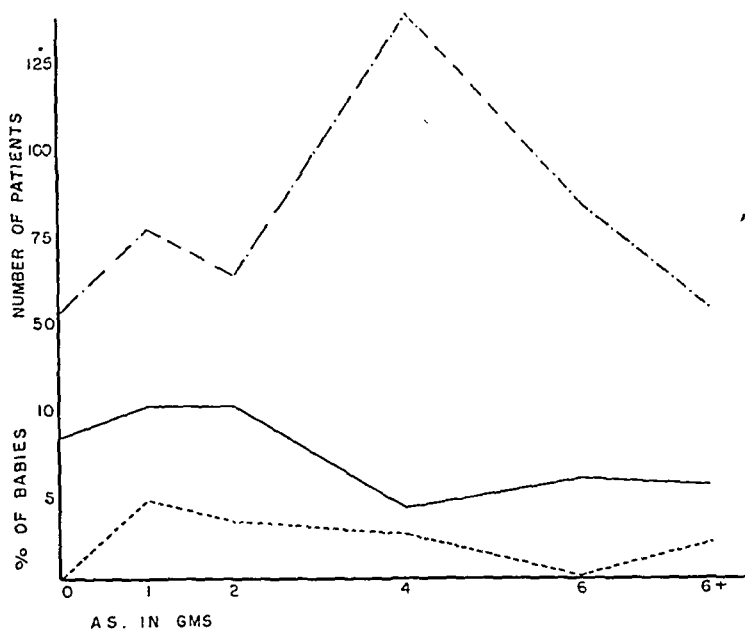


Chart 1.—The distribution of patients, infected fetuses, and fetal mortality with regard to the amount of arsenical therapy received by the mother during the antenatal course. —. —., Number of patients; —, per cent of dead babies; - - - -, per cent of syphilitic babies.

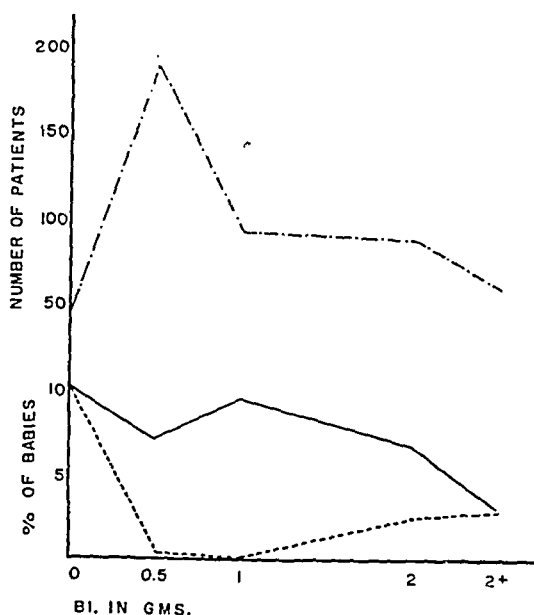


Chart 2.—The distribution of patients, infected fetuses, and fetal mortality with regard to the amount of bismuth therapy received by the mother during the antenatal course. —. —., Number of patients; —, per cent of dead babies; - - - -, per cent of syphilitic babies.

TABLE V. SHOWING THE AVERAGE PLACENTAL WEIGHT AND AVERAGE BABY WEIGHT IN THE TWO GROUPS OF SYPHILITIC PATIENTS AS COMPARED WITH THE TWO ANALOGOUS GROUPS OF NONSYPHILITIC PATIENTS. SIMILAR AVERAGES ARE ALSO SHOWN FOR THE SYPHILITIC BABIES

	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
All babies:				
Average placental weight	636.1	616.5	648.7	611.0
Average baby weight	3223.4	3460.8	3312.2	3549.5
Syphilitic babies:				
Average placental weight	640.0	----	----	----
Average baby weight	3234.0	----	----	----

The placental weights were not consistently different.

The weights of the babies and of the placentas of the group of babies found later to be syphilitic were not significantly different from the remainder of the group.

EFFECT OF TREATMENT

Because of the size of the series and the relatively small number of syphilitic babies found, it is impossible for us to attempt to determine the effects of treatment except in relation to the number of syphilitic babies and the number of fetal deaths occurring in the different treatment groups and the different age groups.

A steadily progressive diminution of syphilitic babies is noted with the increased amount of therapy that the mother received antepartum and only one fetus was found to be syphilitic whose mother received more than 6 grams of an arsenical preparation (Chart 1).

No correlation of total amount of bismuth therapy to the evidence of syphilitic infection of the fetus was noted (Chart 2).

The occurrence of deadborn babies and neonatal fetal deaths was not found to vary directly with the amount of either type of treatment received. On the contrary, with advancing dosages of both arsenic and bismuth, there was found to be a steady fall in the number of fetal casualties until, with good therapeutic doses of arsenic, a number not exceeding the control level was obtained.

The effect of treatment prior to the pregnancy is of considerable interest and importance (Table VI).

It is worthy of note that no syphilitic babies were obtained in the group receiving treatment both prior to and with the pregnancy, even though a considerable number of these patients received minimal treatment in both instances.

An attempt to correlate the number of dead babies with the presence of previous treatment showed a noticeably lower incidence, seemingly within control levels, for this group, while those receiving no treatment prior to the pregnancy had a noticeably higher fetal mortality rate.

We were unable to correlate the amount of previous treatment with the number of fetal deaths and could find no effect of previous treatment on the fetal mortality of the previous pregnancies.

The time of onset of treatment in the pregnancy was correlated with the incidence of syphilitic and dead babies. The incidence of syphilitic babies was found to decrease significantly as the length of treatment increased. More fetal deaths, however, occurred in patients registering early, although the peak of fetal death was noted later in the control group and fell below the syphilitic group approaching term (Chart 3).

INFLUENCE OF THE AGE OF THE PATIENT

We attempted to correlate the incidence of dead and syphilitic babies with the age of the infection, using the age of the patient as a rough index of the duration of the infection in the mother. It seemed quite obvious that the higher

TABLE VI. SHOWING THE EFFECT OF PREVIOUS TREATMENT ON THE OUTCOME OF PREGNANCY

	SYPHILITIC PATIENTS		CONTROLS
	WITH PREVIOUS TREATMENT	WITH NO PREVIOUS TREATMENT	
Number of pregnancies	260	193	500
Babies followed	123	88	---
Syphilitic babies	0 (0.0%)	9 (10.2%)	---
Dead babies	17 (6.5%)	16 (8.4%)	29 (5.8%)

COMPLICATIONS OF PREGNANCY

Dystocia, pyelitis, and ante-partum bleeding were not noted to have an increased frequency in either syphilitic group. Three patients delivered hydatidiform moles, an incidence of 0.66 per cent of the total group. Toxemia of pregnancy, however, was found to have a real increase in incidence, although this increase could not be correlated with the amount of treatment nor with the time it was begun, nor with the amounts of arsenic or bismuth received (Table VII). It would seem that the lower incidence in the Berwind syphilitic group as compared with the controls in that clinic merely means that a greater percentage of these patients had been sent to the New York Hospital.

TABLE VII. SHOWING THE INCIDENCE OF TOXEMIA IN SYPHILITIC AND CONTROL GROUPS

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Total pregnancies	192	261	200	300
Cases with toxemia	29	8	15	14
Per cent with toxemia	15.1	3.1	7.5	4.7

DISCUSSION

The incidence of dead and syphilitic babies in this series is very small and well bears out the clinical impression that syphilis need be no longer the primary cause of death in the fetus nor a frequent disease in the newborn.

McCord¹⁹ has shown that the previous pregnancies which occurred in his series of patients had resulted in large numbers of disastrous terminations, and untreated syphilitic patients have been shown⁸ to have a comparably high fetal mortality rate. The group of pregnancies in our previously untreated patients showed 65 to 75 per cent living babies and no significant difference could be made out when compared with previous pregnancies of the group which had been treated sometime previously.

The outcome of the present pregnancies corresponds well with figures previously reported for treated series.⁷⁻⁹ Although the incidence of stillbirths is slightly higher than that in a similar group of control patients, this difference is not alarming, and the low incidence of infected babies is most gratifying.

One explanation for this lowered mortality and incidence of fetal infection is obviously antenatal therapy. The treatment received prior

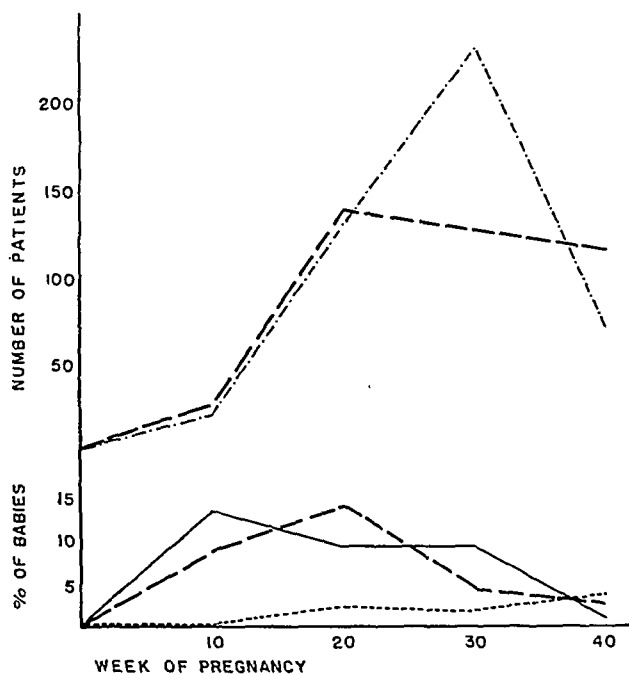


Chart 3.—The distribution of syphilitic and control patients, infected fetuses, and fetal mortality in both the syphilitic and control groups with regard to the week of pregnancy in which registration occurred or in which treatment was started. —, Number of syphilitic patients; ---, number of control patients; ———, per cent of syphilitic babies; ———, per cent of dead babies in the syphilitic group; ———, per cent of dead babies in the control group.

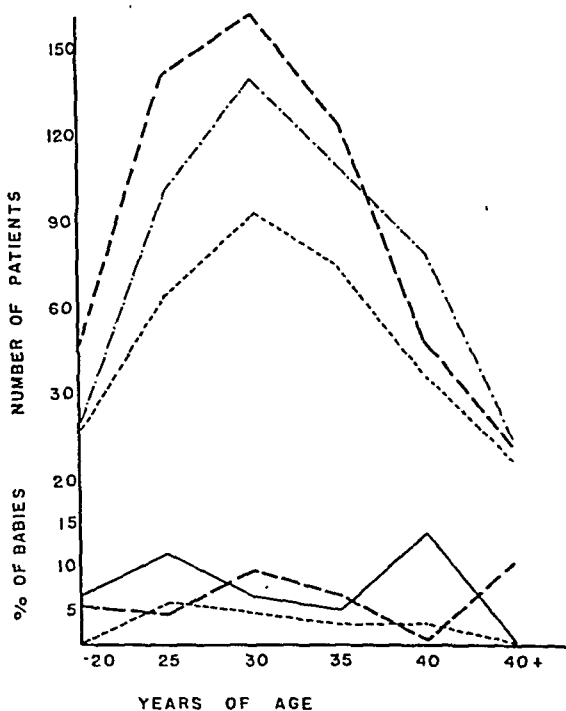


Chart 4.—The distribution of syphilitic and control patients, infected fetuses, and fetal mortality in both syphilitic and control groups with regard to the age of the mother at the time of delivery. —, Number of syphilitic patients; ———, number of syphilitic patients whose babies were followed in pediatrics; ———, number of control patients; ———, per cent of syphilitic babies; ———, per cent of dead babies in the syphilitic group; ———, per cent of dead babies in the control group.

TABLE VIII. GIVING PERTINENT DATA ON BABIES FOUND TO BE SYPHILITIC THROUGH PEDIATRIC FOLLOW-UP

MOTHER					BABY							MOTHER'S TREATMENT				COMMENT
CASE	RACE	AGE	PARITY	DIAGNOSIS	WASSERMANN	CONDITION AT BIRTH	CORD WASSERMANN	X-RAY OF LONG BONES	PLACENTAL PATHOLOGY	DIAGNOSTIC CRITERION	PEDIATRIC FOLLOW-UP	PRIOR TO PREGNANCY	DRUG	AMOUNT	DURATION OF OBSERVATION IN WEEKS	
13	White	24	ii	Latent	4+	Living Term	4+	Sug- ges- tive	Neg.	Clin.	1½ yr.	0	Neo. Bi.	3.6 2.3	19	Baby: Lymph nodes and spleen palpable. X-ray showed periostitis for 6 wk. Wass. 6 wk. +; neg. with treatment 1½ yr. Mother: No lapse in treatment during this pregnancy. First pregnancy resulted in mole and abortion. Wass.: 6 wk. +; neg. with treatment 1½ yr.
76	White	24	ii	Latent	Wass. neg. Kline 4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	As.	1.7	16	Baby: Snuffles. Wass.: 6 wk. 4+; neg. with treatment 2 yr. Mother: No lapse in treatment during this pregnancy. First baby died at 3 months of "cold." Wass.: 6 wk. neg.; treatment for 3 yr. following.
96	White	23	i	Latent	4+	Living Term	Wass. neg. Kline 4+	Sug- ges- tive	—	Clin.	3 yr.	0	Neo. As.	1.6 0.6	8	Baby: Questionably syphilitic. X-ray showed periostitis. Wass.: neg. 6 wk. and 2 yr. Kline 4+ even 4 yr. later. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. -2+; neg. with treatment 2 yr.
97	Col.	31	i	Latent	4+	Living Term	—	Syph- ilic	—	Clin.	3 yr.	0	As. Bi.	2.2 1.6	30	Baby: Questionably syphilitic. Bones showed thickening of the periosteum for 7 months. Wass.: neg. 6 wk. and 2 yr. Mother: Lapse in treatment for last 1½ months of this pregnancy. Wass.: neg. 6 wk. and 2 yr. Treatment 4 months following.

to pregnancy certainly plays a fundamental part. The fact that a large number of patients who had received minimal amounts of treatment during the pregnancy, prior to it, or both, and still had a satisfactory outcome suggests that a fair number of these patients had received their infection very early in life, and that it had become attenuated with the passage of time prior to conception.¹¹ It is also possible that the disease itself has become less virulent since the advent of modern therapeutic methods.

The only method we have considered as absolute in the diagnosis of syphilis in the fetus is a pediatric follow-up of six months or more, and to this have been compared other generally used methods. Although this period of time is probably not sufficient to be absolute, it is felt that the small number of babies who might develop positive serology or clinical symptoms and signs following this time would not materially alter our statistics.²⁰

An attempt to follow all babies from eighteen months to two years was made and failure to report for clinic appointments was vigorously investigated by the Social Service Department. Loss of cases in the follow-up was more evident in the non-syphilitic group than in the syphilitic group since more effort was made to follow the baby where doubt was felt for the syphilitic status than where the nonsyphilitic status was considered relatively certain.

The findings of the x-ray of the long bones, placental histology, and cord Wassermann bear out this faith in the pediatric follow-up and the real lack of specificity of any or all of the other means of diagnosis.

The relative value of the x-ray diagnosis is of course colored by individual interpretation of the films; and antisyphilitic and other types of medication (particularly bismuth), varying bone densities and poor plates all probably decrease their reliability. Numerous types of bone abnormalities have been shown to be confused with the type of lesions produced by syphilis.^{15-17, 21}

Although placental histology as a diagnostic aid to congenital syphilis has been time honored,¹⁸ it has not been generally recognized that the typical picture was originally applied only to macerated fetuses.²² Here again individual interpretation plays a great part in the diagnosis.²³⁻²⁵ It also seems obvious that extraneous factors such as prematurity and vascular diseases of the placenta which are nonsyphilitic in origin may serve to produce the same picture.

The cord Wassermann seems to be of value as an absolute diagnostic aid in congenital syphilis only when it is positive and the maternal blood Wassermann is negative. It is recognized, however, that a fetus born with a negative cord Wassermann may develop syphilis.

Although this series and those previously reported bear out the fact that the x-ray of the long bones, placental histology, and cord Wassermann more often show the so-called pathognomonic changes when the baby is syphilitic,⁷⁻⁹ it is also significant that none of the criteria are absolute. Also the baby may be syphilitic but show none of these signs.

It has also been noted that the reagin titer of the baby's blood may remain high for much longer periods of time than have been generally accepted,²⁶ while the fetus may still fail to show signs of syphilis after prolonged follow-up. These observations tend to suggest that syphilis should be neither diagnosed nor treated until sufficient observation has been carried out.

This series confirms the previous work that a patient who receives more than 4 Gm. of arsenic has less than a 5 per cent chance of bearing a syphilitic child.⁹ Even more than 6 Gm. during the antenatal course, however, do not absolutely insure a nonsyphilitic fetus.¹⁰

The reduction in fetal mortality and infection associated with the early onset of treatment is quite evident in this series as in the previously reported patients.⁸⁻¹⁰

Treatment received both prior to and during pregnancy produces the most striking and reliable effect on fetal incidence of infection and mortality. Although this finding has been previously described,^{8, 10} its real significance has not been appreciated by many physicians treating pregnant women. Among these patients of our series, no syphilitic infections were noted and the fetal mortality was comparable to that of the nonsyphilitic, nontreated controls.

One of the original purposes of this study was to determine what effect treatment alone played in the production of fetal mortality. In taking that group in which the incidence of syphilitic infection of the fetus is at a very low figure (patients who had received treatment prior to and during this pregnancy), we find that the mortality rate is quite comparable to that of a similar group of normal, nonsyphilitic patients in whom no treatment has been carried out. This is also borne out by the low mortality rate of fetuses whose mothers have received early and adequate treatment.

The high incidence of fetal mortality and fetal syphilitic infection in the group receiving minimal amounts of therapy suggests that this mortality is due to syphilitic infection of the fetus. This would also tend to show that if antisyphilitic therapy causes fetal death (which we cannot demonstrate), it occurs as in the adult as a sensitivity reaction in the early course of treatment, and therefore no real advantage would be obtained by giving the suspected mother a few treatments for prophylaxis of the child.

It is known that the patients with old infections have less tendency to transmit the disease to the fetus,¹¹ and our figures, using the age of the patient as an index to the duration of infection, tend to substantiate this finding. However, since most of these patients have no knowledge of the duration of the infection, it is unsafe to use age as a basis for giving or withholding treatment.

There seems to be a significant rise in fetal mortality in the earlier age groups, and also in the elderly patients. Cole⁹ has postulated that the early rise is due to the activity of a recent infection, and the rise of fetal mortality late in life is similar to that described in control patients

104	White	28	i	Latent	3+	Living Term	—	Neg.	Neg.	Clin.	1 yr.	0	As.	1.3	9	Baby: Definitely syphilitic. Wass.: neg. 6 wk.; 6 months 4+. Not followed after 6 months. Mother: No lapse in treatment during this pregnancy.
127	White	39	viii	Late latent	4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	Neo. Bi.	0.6 0.4	20	Baby: Long bones showed increased density adjacent to the epiphysis at 3 yr. Wass.: 6 wk. 4+; 2 yr. neg. Treatment 1½ yr. Mother: Lapse in treatment for last 1½ months of this pregnancy. Three spontaneous abortions at 8 wk. Wass.: 6 wk. and 2 yr. 4+. Treatment 3 yr. following.
140	Col.	29	i	Latent	4+	Living Term Twins	A. 4+ B. —	Neg. Neg.	Neg. Neg.	Clin. Clin.	2 yr. 2 yr.	0	As. Bi.	1.8 1.6	15	Babies: Wass.: 6 wk. 4+; 2 yr. neg. Treatment 1½ yr. Mother: Lapse in treatment for 5 months in the middle half of pregnancy. Wass.: 6 wk. and 2 yr. 4+. Treatment 3 yr. (Wassermann fast.)
146	White	31	iii	Latent	4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	Neo. As.	0.3 0.6	7	Baby: Wass.: 6 wk. 4+; neg. 2 yr. Treatment 1½ yr. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. 4+; 2 yr. 3+. Treatment 4 yr. Still being treated.
183	White	32	iv	Early latent	3+	Living	—	Pos.	Neg.	Clin.	1 yr.	0	As. Bi.	7.05 3.2	12	Baby: Petechiae of skin; desquamation of soles of feet and palms of hands; secondary syphilis diagnosed at birth. Wass.: 4 wk. 4+; neg. at 6 wk. following beginning of treatment. Spleen palpable. Long bones showed lines of linear density at the metatarsals suggesting treated prenatal syphilis. Treatment 1 yr. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. and 1 yr. 4+. Treatment 1 yr. Still being treated.

PSYCHIATRIC CONTRAINDICATIONS IN THE USE OF ESTROGENS DURING THE MENOPAUSE

W. LYNWOOD HEAVER, M.D., WHITE PLAINS, N. Y.

(From the clinical services of The New York Hospital, Westchester Division)

THE therapeutic management of the nervous menopausal female offers a challenging problem. Novak¹ has warned the physician not to be hasty in blaming a woman's climacteric experience for any peculiar symptom complex that defies usual diagnostic methods. After satisfactorily ruling out possible organic factors, attention may then be directed toward the menopause and its attendant ovarian insufficiency.

Investigators have demonstrated the efficacy of natural hormone substitutive therapy in cases of menopausal endocrine imbalance, but it should be noted that such reports emphasize that the beneficial effects are greatest in cases presenting *vasomotor* signs and symptoms. Werner² has written that the most frequent features of menopausal aggravation are: "excitability, irritability, headache, occipitocervical pain, crying, decreased memory and concentration, depression psychosis, and formication." These, with insomnia, are grouped by him under *nervous* manifestations. He lists the *circulatory* complaints in this order: "hot flushes, tachycardia, palpitation, dyspnea, vertigo, scotomata, cold hands and feet, numbness and tingling." These two categories, together with alterations in the established menstrual pattern, constitute the menopausal syndrome.

In determining a particular therapy for the menopausal patient, such listings as the above deserve close scrutiny. In middle-aged women, as these nervous symptoms are encountered, considerable variation is noted, both as to intensity and the subjective attitude of the patient toward them. A great deal of the irritability, depression, etc., is contingent upon the presence of hot flushes and other bizarre somatic sensations. Hence, the physician, whatever may be his specialty, is likely to be confronted by a few patients whose emotional balance has been notably affected by their distress over their hot flushes and other neurocirculatory symptoms. Novak states that only a small minority of menopausal females suffer notably from vasomotor complaints.¹

In such a group as the latter, the careful use of any legitimate estrogenic preparation which has been demonstrated to abolish or minimize vasomotor symptoms is good treatment. And, so far as the patient's exaggerated emotional response is related to these vasomotor phenomena, the estrogens may be expected to aid the patient in regaining her psychic equilibrium. The doctor will aid her by such prescription with greater success provided her psychic turmoil is circumstantial rather than definitely systematized. Papanicolaou and Shorr³ have called attention to this likelihood in their work on the action of ovarian follicular hormone in the menopause. Studying the patient's response

by Sterling.²⁷ Our control figures do not bear out either rise, but it seems likely that our figures in both the very young and the very old groups may not be significant, due to the small number of patients.

We are unable to explain why the toxemias of pregnancy occur more frequently in the syphilitic than in the nonsyphilitic patients. It is perhaps significant that 70 to 80 per cent of the toxemic patients had positive Wassermans but previous treatment or the amount and type received during the present pregnancy could not be correlated with the incidence of toxemia.

The incidence of hydatidiform mole was higher in this group of syphilitic patients than in the clinic as a whole.

CONCLUSIONS

Syphilis need no longer constitute a major cause of fetal mortality or a frequent disease of the newborn.

Antenatal therapy, which is responsible for the greater part of this effect, is greatly enhanced by treatment received prior to conception.

A favorable outcome is made more certain by early institution of treatment, advanced age of the infection, and negative serology.

No definite fetal mortality rate could be associated with adequate antenatal therapy.

The only satisfactory and reliable criterion of congenital syphilis in the infant is repeated clinical, serologic, and radiologic examination for a period of months or years following delivery.

The incidence of toxemia of pregnancy and of hydatidiform mole is definitely elevated in the syphilitic patient.

The authors wish to take this opportunity to thank Miss Gertrude Skelley, R.N. who has been largely responsible for making available reliable records on those patients seen at the John E. Berwind Free Maternity Clinic and to Dr. William L. Fleming, University of North Carolina School of Public Health, Chapel Hill, North Carolina, for aid and suggestions which have been invaluable.

REFERENCES

- (1) *Leblanc, R. F.*: Quoted in Special Article, *Ven. Dis. Inform.* 6: 360, 1925.
- (2) *Hochsinger, Karl*: *Wien. klin. Wchnschr.* 23: 881, 1910. (3) *Idem*: *Ibid.* 23: 932, 1910. (4) *Williams, J. W.*: *Bull. Johns Hopkins Hosp.* 31: 141, 1920.
- (5) *McCord, J. R.*: *J. A. M. A.* 88: 626, 1927. (6) *Wile, U. J., and Shaw, J. W.*: *Ibid.* 95: 1791, 1930. (7) *McCord, J. R.*: *Am. J. Syph.* 16: 78, 1932. (8) *McKelvey, J. L., and Turner, T. B.*: *J. A. M. A.* 102: 503, 1934. (9) *Cole, H. N., and Clinical Cooperative Group*: *Ven. Dis. Inform.* 15: 83, 1934. (10) *Hillis, D. S., and Benensohn, S. J.*: *Surg. Gynec. Obst.* 66: 54, 1940. (11) *Gammeltoft, S. A.*: *Am. J. OBST. & GYNEC.* 15: 747, 1928. (12) *Editorials*: *Am. J. Syph., Gonorr. & Ven. Dis.* 23: 518, 1939. (13) *Ingraham, N. R.*: *J. A. M. A.* 112: 1537, 1939. (14) *Moore, J. E.*: *Bull. Johns Hopkins Hosp.* 34: 89, 1923. (15) *McLean, S.*: *Am. J. Dis. Child.* 41: 130, 1931. (16) *Idem*: *Ibid.* 41: 363, 1931. (17) *Idem*: *Ibid.* 41: 607, 1931. (18) *Frankel, Ernst*: *Arch. f. Gynäk.* 5: 1, 1873. (19) *McCord, J. R.*: *J. A. M. A.* 105: 89, 1935. (20) *Roberts, M. H.*: *Am. J. Dis. Child.* 45: 461, 1933. (21) *Caffey, J.*: *Am. J. Roentgenol.* 42: 637, 1939. (22) *Browne, F. J.*: *Brit. M. J.* 2: 250, 1927. (23) *Stemons, J. M.*: *Am. J. M. Sc.* 153: 212, 1917. (24) *McCord, J. R.*: *Am. J. Syph.* 16: 83, 1932. (25) *Montgomery, T. L.*: *Am. J. OBST. & GYNEC.* 31: 253, 1936. (26) *Christie, A. U.*: *Am. J. Dis. Child.* 55: 979, 1938. (27) *Sterling, E. B.*: *Pub. Health Rep.* 46: 207, 1931.

whose personal attributes are suggestive of the pre-psychotic personality of an involuntional melancholia patient do not become mentally ill. At least they do not enter mental hospitals. The known existence of ovarian insufficiency in all menopausal women makes it difficult to state that such deficiency is the *x* factor which determines whether or not a woman in her climacteric will become psychotic. However, this attitude is reflected in the writings of those^{8, 9} who advocate substitution therapy for involuntional psychoses as though it did not matter if vasomotor phenomena were present or not, and that the presence of labyrinthian psychic conflict is purely incidental.

Not infrequently a woman who has passed through her menopause without subjective distress will, five or ten years later, become psychotic. The history and features of her illness are such that a diagnosis of involuntional melancholia is made. Papanicolaou and Shorr note that: "The menopausal type of (vaginal) smear is invariably present after the menopause, whether or not symptoms exist."³ Regarding our patient above, the psychiatrist might paraphrase their statement: "The basic pre-psychotic personality exists before, during and after the menopause, whether or not a psychosis occurs." When the psychosis happens during the climacteric, the emotional trauma to that particular personality of the menopause experience itself, in a setting of heightened emotional response, may be the trigger mechanism for the psychosis. It follows, then, that the endocrine imbalance known to exist during physiologic gonadal involution may contribute to the emotional hypersensitiveness observed in the menopausal female. Substantiation of this is recognized when the diagnosis of involuntional melancholia is made also in the psychotic male who is obviously in his involuntional era. His pre-psychotic personality type characteristics are, broadly, the same as those of the female with the same psychosis.

In other words, to the menopausal female or the impotent male their physiologic involution assumes a symbolic significance. With emotional hypersensitiveness as a background, the stage is set, so to speak, so that emotional and personality factors are free to engage in a conflict marked by deep introspection, delusions, guilt-feelings, agitation, and depression.

It is common knowledge that such a woman is much more susceptible to minor insults to her pride or ego, and certainly she experiences more difficulty than ever before in coping with these, as well as with her major consciously recognized and/or long repressed emotional content of thought. Should the production of exaggerated affective responses be due to ovarian endocrine deficiency, as some workers believe,⁸⁻¹⁰ it is a short step, according to such hypothesis, to indict the same mechanisms as the etiologic agent for the more profound gross mental aberrations we are discussing. Obviously, such emphasis entirely neglects the most cogent element in the psychotic pattern so produced: the basic pre-psychotic personality type, including early and later aspects. Brew and Davidoff have demonstrated that both the recent and remote personality features are etiologically important.

It is also true that the involuntional era in a woman often marks the recurrence of one phase or the other of a manic-depressive illness . . .

to estrogen by means of periodic vaginal smears, they "repeatedly found severely psychoneurotic patients highly resistant to treatment both as regards smear changes and symptomatic relief." The authors felt that this indicated some relationship between the menopausal syndrome and the psychic states noted during the climacteric.

Psychiatrists occasionally find it difficult to distinguish between the involved psychoneurotic and the actual psychotic patient. The menopause experience is capable of precipitating a profound mental disorder (psychosis): *involutional melancholia*. This type of mental aberration has been estimated as comprising from 3 to 4 per cent of all mental disease. Psychoses of other varieties are known to have their incidence in the climacteric era. Psychiatrists have long differentiated organic, affective (emotional; "benign") and schizophrenic (tend; "malignant") illnesses. Involutional psychoses, either the melancholic or paranoid types, fall into the affective grouping, as do the manic-depressive disturbances.

In 1897 Kraepelin called attention to the syndrome of involutional melancholia and regarded it as distinct from the other great affective class of manic-depressive disorders. However, he later signified agreement with his pupil, Dreyfus, when the latter, in 1907, returned the involutional syndrome to the manic-depressive category. Shortly thereafter, in a masterful evaluation of Dreyfus' work, Kirby⁴ re-established the syndrome as a distinct clinical psychiatric entity. Since that time other observers⁵⁻⁷ have augmented Kirby's contribution until today we recognize that marked agitation and depression, absurd delusional ideas, together with profound guilt-feelings constitute the psychotic menopausal (involutional) syndrome. In this illness, the menopausal or post-climacteric female is seen to be typically characterized as one who for years has been essentially selfish, narrowed in her interests, over-religious, frigid sexually or poorly adjusted to the sexual aspect of her marriage, narcissistic, and remarkably rigid in her social, moral, and ethical attitudes. Together, these attributes may be summated in the term "pre-psychotic personality." Such characteristics are not found so consistently or frequently among other women in the same physiologic era who develop a manic-depressive or a schizophrenic illness.

With the onset of a true involutional psychosis (melancholia), she becomes worried and depressed in spirits. She cannot sleep, is hypochondriacal, and preoccupied with somatic delusions. Finally she refuses to eat. When asked the reasons for her behavior and state of mind she offers bizarre absurdities that reveal her delusional and guilt-feelings.

It is largely this latter feature, the sense of guilt, real or delusional, over past minor and major infractions of her rigid code of behavior, and the agitation, which sets her apart from her depressed manic-depressive fellow-patient. Such autflagellation of her emotional self-control results in an involved illness of many months' duration. When the delusional content is of a paranoid variety, the prognosis is less favorable.

A vast number of women go through the menopause with little or no subjective vasomotor complaints.¹ Of these, an overwhelming majority

In addition to the substitutive aspect, estrogen preparations play a *stimulative* role when given, in adequate amounts, to the menopausal female. For this reason the physician should be exceedingly careful in his selection of patients for hormonal therapy. I agree with Brew and Davidoff in their belief that estrogens "may at times prove harmful if administered indiscriminately."

Our experience with psychotic menopausal and postclimacteric women at the New York Hospital, Westchester Division, White Plains, has led us to believe that a wrong and dangerous emphasis has been given to past and current conjectures of investigators regarding the value of ovarian hormonal therapy in the treatment of menopausal *mental* disorders. Repeatedly it has come to our attention that the unwitting physician in practice has attempted to treat his greatly upset neurotic menopausal or psychotic involutional patient with endocrine preparations when such patients have not been bothered by the usual neuro-circulatory symptoms constituting the menopausal syndrome.

Under the circumstances just described, experience has demonstrated conclusively that among such severely neurotic, mildly or profoundly psychotic patients, hormonal therapy not only fails to help the patient but usually increases the emotional chaos the physician is trying to combat. This arises from the stimulation, by the estrogen, of ovarian and genital activity. These patients are, by virtue of their previous personality, in great conflict over their psychosexual desires and attitudes.

We recently had opportunity to check accurately this impression by experimental procedure in an effort to test the potency of a new synthetic ovarian follicular hormone* not yet available for general use. Twenty-six patients were selected for the study because their mental disorder had its incidence in the menopausal era, or subsequent to it, and was accompanied by many of the nervous symptoms outlined by Werner as being commonly associated with the menopausal syndrome; however, in contrast to similar studies made by other observers, it is of interest that none of them complained of the vasomotor phenomena of "hot flushes."

Of the 26 cases, 7 women had involutional melancholia, one had an involutional psychosis, paranoid type, while 15 were diagnosed as suffering from other psychoses. Two women had paranoid dementia precox (schizophrenia), while one was a Korsakoff's syndrome (alcoholic psychosis). The synthetic hormone's potency and general similarity to the natural estrogens was indicated by the production of "withdrawal bleeding" in 60 per cent of these patients with previous amenorrhea (one patient had not menstruated for twenty years), and by the alterations of the vaginal epithelium architecture as revealed by periodic vaginal smears. In six cases, or 23 per cent, certain so-called "toxic side-effects" were also noted: sensation of fullness in breasts, with enlargement, deeply-pigmented tender nipples and areolae, sensation of vulvar fullness, increased sexual desire, transient nausea, dysmenorrhea, persistent nausea, and diarrhea.

*4,4'-dihydroxy- α , β -diethyl stilbene (stilbestrol). Acknowledgment is made to E. R. Squibb & Sons for generous supplies of stilbestrol.

possibly due to the same setting of emotional acuity which encourages the development of involuntional melancholia. But, as has been shown, the prepsychotic type of the involuntional melancholia patient is quite different from that of the woman who relapses into a manic-depressive illness. The previous attack of the manic-depressive patient has occurred, oftentimes, many years before the menopause. No ovarian insufficiency was operating then. Some other factor(s) precipitated the psychosis. And, it is so frequently seen in the reactivation of such an illness during or following actual menopause that emotional trauma has again precipitated the psychosis. To either type of potentially psychotic female such trauma may be the experience of the menopause itself . . . and all that it implies to the woman: loss of reproductive function, onset of middle age, etc. She may think of herself as a woman whose effective work in life has been completed and whose brightness in the family constellation is considerably dimmed.

It is generally recognized that involuntional melancholia or involuntional paranoia is preceded by a very long prodromal period, often of many years' duration.⁶

Again we emphasize that the minimization of hot flushes, chilly sensations and palpitations will cause the patient to be notably less disturbed *so far as she is disturbed over their presence*, and this improvement may aid her in taking a less distraught attitude toward her emotional conflicts. But this degree of improvement cannot be objectively regarded as setting the patient free from the shackles of her psychosis. Moreover, the occurrence of a menopausal psychosis (involuntional melancholia) in a woman who does not complain of vasomotor nor sympathetic nervous system disturbances raises the question if the *x* factor, whatever it may be, is properly assigned solely to the field of endocrinology. Dynes¹¹ reports, significantly, the case of a woman whose vasomotor symptoms were relieved and her psychosis soon improved under endocrine therapy. She returned home; her hormone treatments were shortly discontinued and she soon suffered a recurrence of her hot flushes and other sensations. Likewise, she became considerably involved psychically. Upon returning to the hospital, she was given estrogen and her vasomotor symptoms disappeared, but her psychic aberrations continued more or less unabated.

Brew and Davidoff,⁷ in an admirable discussion of the involuntional psychoses mention that endocrine therapy cannot be expected to prevent or to cure a menopausal psychosis, because "where the individual's reaction to the menopause and its somatic influence is preponderantly affected, it allays only one factor in the total picture, not the superimposed one." They feel that the chief value of estrogens is seen in early *substitutive* therapy, in cases "where estrogenic or endocrine factors predominate in producing neurotic symptoms." Corroborating Shorr's comment previously mentioned, Brew and Davidoff point out that even among these cases, where the neurotic reaction pattern is influenced by the previous personality of the patient, little can be expected from substitutive hormonal therapy.

ROENTGEN VISUALIZATION OF THE PLACENTA BY SOFT TISSUE TECHNIQUE

A REPORT OF TWO YEARS' EXPERIENCE

A. LOUIS DIPPEL, M.D., AND WEBSTER H. BROWN, M.D. BALTIMORE, Md.

(From the Departments of Obstetrics and Roentgenology, Johns Hopkins University and Hospital)

IN PREVIOUS articles,^{1, 2} we have reviewed the literature dealing with localization of the placenta by various clinical and roentgen methods and have recorded our earlier experiences with direct visualization of the placenta by the use of the technique first described by Snow and Powell,³ but used also for some years by Smith⁴ who has as yet not published his results. After employing this method for a period of two years in 262 examinations, it seemed desirable for us to analyze our results statistically in an effort to determine the clinical value of this method.

It will be recalled that the method requires no preparation of the patient such as the injection of radio-opaque dyes into the urinary bladder or blood stream. It is entirely dependent upon actual visualization of the placenta on a lateral roentgenogram obtained with a technique that is not essentially different from conventional roentgenography. We have employed aerocystography in certain instances and occasionally confirmatory information has been obtained, but this report is based solely upon the primary method of actual visualization of the placenta. The location of the placenta can be easily determined in Fig. 1, since here the placenta is markedly calcified. We have not observed sufficient calcification actually to visualize the whole placenta in any of the other 261 examinations. However, in 6 there was slight (2) or moderate (4) calcification, but not sufficient to allow localization of the placenta on this basis alone. Therefore, calcification of the placenta is not an important factor in determining its location by this method. Usually the radiodensity of the placenta so closely approximates that of the uterine wall as to render differentiation of placental and uterine wall shadows impossible. But at the site of placental implantation, the uterine wall appears to be unusually thickened and this forms the basis of localization of the placenta by the soft tissue technique.

RESULTS

In 134 observations on 100 roentgenograms, we have found the average thickness of the uterine wall at the apex of the fundus and at its anterior and posterior walls during the last trimester to measure 1.24 cm. Snow and Powell³ have shown that the combined placental and uterine wall shadow measures approximately 7.0 cm. at the point of greatest thickness and tapers off toward the periphery of the placenta. A typical example of this picture is shown in Fig. 2 where the placenta is clearly visualized on the posterior wall of the fundus. It is inconceivable that other soft tissue uterine or intrauterine shadows would be misleading or would introduce factors of doubt. It would be exceedingly rare, if possible, that an intramural or submucous

Bearing in mind the criticism by investigators who believe an involutional psychosis is due entirely to endocrine insufficiency, that poor therapeutic results with estrogen stems from inadequate dosage, the amounts of the synthetic hormone prescribed were considerably in excess of any as yet reported in the literature.

I recognize that many of the unfavorable toxic side-effects obtained with this particular preparation are not ordinarily perceived with the usual dosage of the natural hormone; however, it has been my experience that such effects as increased sexual desire and vague feelings of discomfort in the genital area are not uncommonly found with the moderate dosages of natural hormones now on the market.

Among the 12 patients (46 per cent) who showed no obvious awareness and/or offered comments attributable to the "withdrawal bleeding," such remarks were definitely of an unfavorable nature among 8 patients and conceivably favorable among 4.

The psychiatric clinical course during treatment revealed that 67 per cent remained unimproved and that 4 per cent became much worse.

A comparison of the patient's status before hormonal treatment began with the clinical picture following termination of treatment revealed that 43 per cent remained unchanged and that 38 per cent had become definitely worse. Of the 15 per cent that improved sufficiently to leave the hospital, it may be said that statistically the probability was in favor of ultimate recovery without any specific chemotherapy or endocrine administration.

CONCLUSIONS

The crux of the controversy hinges upon the question of whether the relief of the more aggravating vasomotor symptoms is justifiable at the expense of increasing or exaggerating certain other physiologic aspects which contribute to the psychosexual conflict that is partly responsible for the development of the psychosis or of the involved psychoneurotic burden.

It is our belief that it is not; and among such cases as are not characterized by distressing vasomotor phenomena, the employment of hormonal therapy solely to "cure" the mental aberrations of the involutional period appears entirely unjustifiable.

REFERENCES

- (1) *Novak, E.*: J. A. M. A. 110: 619, 1938.
- (2) *Werner, A. W.*: Endocrinology, Philadelphia, 1937, Lea & Febiger, p. 24.
- (3) *Papanicolaou, G. N., and Shorr, E.*: AM. J. OBST. & GYN. 31: 806, 1936.
- (4) *Kirby, G. H.*: N. Y. State Hosp. Bull. 1: 45a, 1908-1909.
- (5) *Titley, W. B.*: Arch. Neurol. & Psychiat. 36: 19, 1936.
- (6) *Palmer, H. D., and Sherman, S. H.*: Ibid. 40: 762, 1938.
- (7) *Brew, M. F., and Davidoff, E.*: Psychiatric Quart. 14: 2, 1940.
- (8) *Hawkinson, L. F.*: J. A. M. A. 111: 390, 1938.
- (9) *Maser, C., and Israel, S. L.*: Med. Clin. North America 19: 205, 1935.
- (10) *Frank, R. T., Goldberger, M. A., and Salmon, U. J.*: N. Y. State J. Med. 36: 1363, 1936.
- (11) *Dynes, J. B.*: Arch. Neurol. & Psychiat. 42: 248, 1939.

Thus far, soft tissue lateral roentgenograms have been obtained on 259 patients; each of two patients were studied in a subsequent pregnancy, and a third patient was observed at two stages of a single pregnancy, making a total of 262 roentgen observations. These patients grouped according to race represent 149 colored, 87 white ward, and 23 private (white) patients. Eighty-seven examinations were upon primigravidas, 61 upon secundigravidas, and 114 upon patients of greater parity. The mean duration of pregnancy for the whole group at the time of x-ray study was 35.5 weeks with the range from 23.0 to 42.5 weeks. The figures for the group



Fig. 2.—Soft tissue lateral roentgenogram of a young primigravida with a normal pregnancy, taken at term for experimental purposes, in order to develop the technique. The placenta is easily visualized on the posterior wall of the fundus. A lateral rather than the ventral surface of the fetus is directed toward the placenta. Osseous structures of mother and fetus are as clearly visualized as in conventional roentgenograms.

showing vaginal bleeding (92 cases) are somewhat less with a mean duration of 34.4 weeks and a range of 23.0 to 41.5 weeks. The eleven instances of actual placenta previa showed an even smaller average duration of pregnancy, 32.2 weeks with a range of 24 to 40 weeks. Contrary to what one might expect, the vaginal bleeding appeared earlier in pregnancy with the lesser degrees of placenta previa; i.e., at an average time of 34 weeks (30 to 40 weeks) in 5 cases of central previa, at 32 weeks (29 and 35 weeks) in 2 cases of the partial type, and at 30 weeks (24 to 35 weeks)

myoma could simulate the shape of the usually observed placental shadow. Retro-placental hemorrhage, as with premature separation of the normally implanted placenta, could not be differentiated from the normally attached placenta but might show increased thickness of the placental shadow. An accumulation of blood in

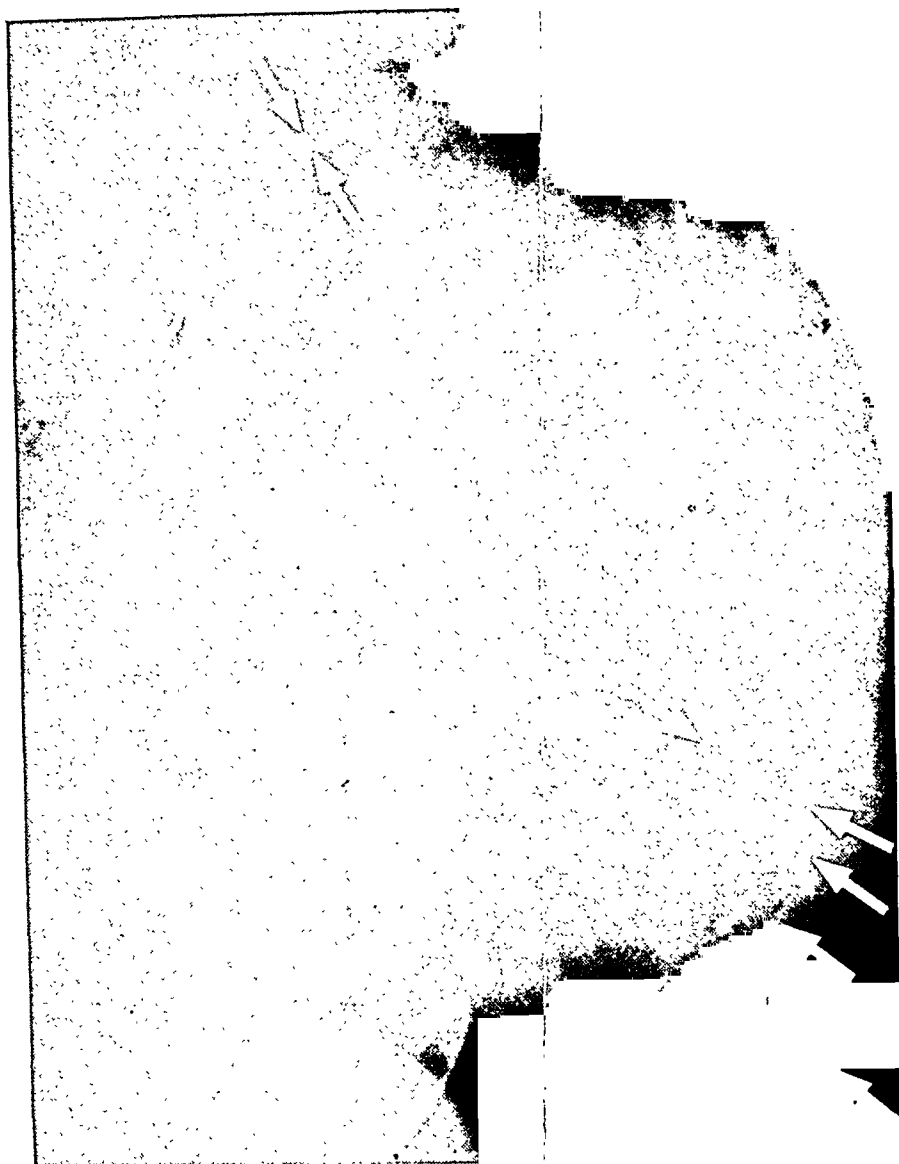


Fig. 1.—Lateral soft tissue roentgenogram of a primigravida obtained in the thirty-eighth week of gestation because of a clinical diagnosis of moderate hydramnios. This shows, instead, a large fetus presenting by the vertex, with its ventral surface facing the placenta, which is implanted over the whole of the anterior wall of the fundus uteri. The placenta can be clearly made out, since it is markedly calcified throughout. The uppermost arrows indicate the thickness of the posterior wall of the fundus; the upper pair of arrows on the anterior wall indicate the thickness of the placenta; the staggered arrows below these indicate in succession, the anterior wall of the fundus uteri, the rectus abdominis muscles, and the subcutaneous with the cutaneous tissues.

the uterine cavity between the chorion and uterine wall might conceivably increase the length of the placental shadow, but it would seem more likely that it would produce a second shadow as with a succenturiate placental lobe. We did not observe variations of this kind in the roentgenograms of the two cases in which a clinical diagnosis of premature separation of the normally implanted placenta was made.

where clinical evidence of premature separation of the normally implanted placenta was present. Therefore, if cesarean section had been routinely performed on all cases of vaginal bleeding on the assumption that they had either placenta previa or premature separation of the placenta, that assumption would have been erroneous and cesarean section would have been unjustifiably performed in 85.87 per cent of the cases.

There is no significant difference in the incidence of implantation of the placenta over the anterior and posterior walls of the fundus, even in instances of vaginal bleeding, but the incidence of implantation over the anterior wall of the lower uterine segment, in our experience, is almost eight times as great as that over the posterior wall of the lower segment. This has been a repeated observation throughout this study, for in only 2 of the 11 cases of true placenta previa did implantation occur over the posterior wall of the lower uterine segment and internal cervical os. Beck and Light⁸ and Jablonski and Meisels⁹ have shown that implantation over the posterior part of the lower segment usually leads to an erroneous diagnosis of normal implantation when observed by indirect placentography. Since that method has a relatively high incidence of accuracy in the diagnosis of placenta previa (provided the pregnancy is advanced and the presentation vertex), we suspect that this indicates a low incidence of posterior wall placenta previa.

TABLE II. LOCATION OF THE PLACENTA AS DETERMINED FROM SOFT TISSUE LATERAL ROENTGENOGRAMS

SEGMENT AND WALL	BLEEDING CASES	NONBLEEDING CASES	TOTAL
Posterior fundus	33	70	103
Posterior lower segment	3	0	3
Anterior fundus	40	67	107
Anterior lower segment	12	11	23
Not visualized	4	22	26
Totals	92	170	262

The placenta was clearly visualized in 236 of the 262 observations, an incidence of 90 per cent. If the 8 examinations from which poor films resulted, had been repeated and granting that satisfactory roentgenograms would have resulted, the maximum visualization obtainable would have been 93 per cent. All causes of non-visualization are listed in Table III, with the interfering factors. Hydramnios has proved to be the greatest interfering factor, but not an important one, since only one of these presented vaginal bleeding as a clinical finding, and placenta previa was not present in that case. Moreover, cases of acute hydramnios usually demand vaginal interference in the way of rupture of the membranes to relieve cardiac and respiratory distress, are frequently associated with fetal anomalies, and the avoidance of vaginal examination is not as urgent as in certain other conditions. Fur-

TABLE III. FACTORS WHICH DETER GOOD VISUALIZATION AND THE INSTANCES OF VISUALIZATION OF THE PLACENTA IN SPITE OF DETERRING FACTORS

DETERRING FACTORS	TOTAL NO.	NOT LOCATED NUMBER	LOCATED	
			NUMBER	INCIDENCE
Hydramnios	18	15	3	16.67%
Immaturity (less than 28 wk.)	13	2*	11	84.62%
Poor films	8	8	0	0.00%
Twin pregnancy	8	2	6	75.00%
Transverse presentation	6	1†	5	83.33%
Extrauterine pregnancy	1	1	0	0.00%
Totals	54	29‡	25	46.30%

*Nonvisualization attributed to (1) poor films and (2) twin pregnancy.

†Cause of nonvisualization included above under hydramnios.

‡Each of above three cases recorded twice.

in 4 of the marginal variety. This point has not been previously touched upon, but our series is so small that the findings may well represent a sampling error.

The indications for roentgenography are listed in Table I. This shows that 92, or 35 per cent, of the examinations were made because of varying amounts of vaginal bleeding, i.e., because of clinical suspicion of placenta previa. The experimental roentgenograms, 47 or 18 per cent, were obtained in the earlier days of this study in order to develop the soft tissue technique. In the event a patient had been previously delivered by cesarean section, it was considered desirable to know whether the placenta in the subsequent pregnancy was implanted over the site of the previous uterine wound, since there is some reason to suspect⁵ that if normal delivery is allowed in such instances, the incidence of rupture of the cesarean scar is higher than if the placenta is implanted elsewhere. In 17 patients in whom delivery by cesarean section was contemplated, the placenta was localized so that if anterior implantation was discovered, the operator might avoid, if he chose to do so, the site of implantation by selecting a low cervical or a classical incision, depending upon whether implantation was over the fundus or over the lower uterine segment. Moreover, he could be forewarned and could avail himself of additional precautionary measures in the way of transfusion. In the remaining 95 instances, 36.2 per cent, the roentgen examination was not requested primarily for localization of the placenta but rather, in most instances, because of suspected abnormality of the pregnancy. The soft tissue technique was nevertheless selected since the resultant roentgenograms furnish equally as good fetal bone detail as conventional roentgenograms and supply the additional information on placental location.

TABLE I. CLINICAL INDICATIONS FOR ROENTGENOGRAPHY

Vaginal bleeding	92
Probable multiple pregnancy	59
Experimental	47
Contemplated cesarean section	17
Previous cesarean section	11
Probable abnormal presentation	9
Probable fetal anomaly	6
Suspected death in utero	6
Hydramnios	4
Suspected postmaturity	4
Myomata uteri	3
Probable erythroblastosis fetalis	2
Unusual maternal obesity	1
Advanced extrauterine pregnancy	1
	262

Torpin,^{6, 7} as well as many an older writer, has shown that the placenta is usually implanted over the relatively flat anterior or posterior uterine wall and that when it extends over the dividing line between anterior and posterior uterine walls, either laterally or across the apex of the fundus, it is likely to be one of a small group of abnormal placentas such as bipartita or spuria. Our relatively small group tends to confirm this impression, for we have never visualized the placenta on both anterior and posterior uterine walls and have never found it absent on both. Table II shows the location of the placenta with reference to segment and wall of the uterus at each examination. Implantation of the placenta on the lower segment was diagnosed whenever all or the major portion of the placenta was visualized in this region and when less than one-half appeared to be implanted above the level of the umbilicus. There were 26 such patients. All of these cases, it is important to note, do not represent clinical cases of placenta previa, nor were they all instances of vaginal bleeding. As a matter of fact, there were only 11 instances of clinical placenta previa in the group, while the remaining 15 were merely roentgenologic instances of low implantation of the placenta. There were only 2 cases

sented by the vertex. Clinical obesity of the mother is not listed as an interfering factor, because we failed to visualize the placenta in only one such instance and here hydramnios was associated.

In their original communication, Snow and Powell³ contended that "in practically all cases, the ventral part of the fetus faces it (the placenta). In no instance was the fetal back flush up against it." We have not found this relationship to be a reliable criterion for location of the placenta. In fact, in at least 4 per cent of our series we would have made an erroneous diagnosis if we had relied upon the fetal position alone to furnish the information on placental location, for in 7 instances in which the fetus presented by the vertex and in 4 in which it presented by the breech, some part of the back of the fetus was directed toward the placenta. Fig. 3 is a typical example of the dorsal surface of the fetus being directed toward the placenta. While it is true that the ventral surface of the fetus frequently faces the placenta, it is not uncommon to see the lateral fetal surface directed toward the placenta.

An attempt to check clinically the location of the placenta, as originally diagnosed by x-ray, was made in 53 (20.4 per cent) of the 261 pregnancies and no roentgen errors were detected. Moreover, in the cases not checked clinically, the subsequent course of the pregnancy and labor was in strict conformity with the roentgenologic diagnosis. The results of the clinical checks are recorded in Table IV. It was considered that placenta previa was present if, on vaginal examination, the lowermost margin of the placenta could be palpated within 5 to 6 cm. of the closed internal cervical os, whereas failure to reach the placental margin at this level was regarded as confirming the roentgenologic diagnosis of "no placenta previa."

TABLE IV. CLINICAL MEANS OF CHECKING THE ROENTGENOLOGIC LOCATION OF THE PLACENTA WITH RESULTS CONFIRMING THE LATTER

CLINICAL METHOD CONFIRMING	NONBLEEDING CASES	BLEEDING CASES	TOTAL
Cesarean section	13	7	20
Vaginal examination	0	31	31
Vaginal examination and cesarean section	0	2	2
Totals	13	40	53

In our hands, the greatest usefulness of the soft tissue technique has been in cases of vaginal bleeding, more particularly in those in which placenta previa could be ruled out, the whole of the placenta being visualized above the level of the iliac crests. There were 81 such patients, making up 88.0 per cent of the cases presenting a history of vaginal bleeding; by means of the method it was possible to spare these women the hazards of an intrauterine digital examination to rule out placenta previa. Of course, vaginal examination may be necessary to determine such causes of vaginal bleeding as cervical, decidual, and placental polyps, erosions of the cervix, vaginal varices, deciduomas, and cervical malignancies, but this can be done by speculum examination and without interfering with the integrity of the cervical canal.

We believe that the method might find some usefulness in determining the relative soundness of the uterine wall in the region of a previous longitudinal cesarean wound, and attempted to visualize anterior wall thickness in 10 patients previously delivered by classical or longitudinal low cervical cesarean section. One of the two in which definite thinning of the anterior uterine wall was found is shown in Fig. 4. In the other instance, the patient was allowed vaginal delivery, and intrauterine examination thereafter revealed a deep furrow in the anterior wall, at the site of the previous classical cesarean section. Only positive findings of this kind will be of value in cases previously delivered by cesarean section, while negative observations will not preclude the absence of a weak cesarean scar. If it were possible to ascertain the site of the previous cesarean incision, and then in the subsequent pregnancy to determine dextro- or levorotation of the uterus, the opportunity to

thermore, the placenta was visualized in three instances in which hydramnios was diagnosed both clinically and roentgenographically. Immaturity is not such a hindering factor as we had previously suspected, for in 2 of 13 instances in which the pregnancy had advanced to only 23 to 27 weeks, nonvisualization in one instance was definitely due to poor roentgenograms and the other was attributed to the multiple pregnancy rather than to the early stage of pregnancy. Fetal position



Fig. 3.—Roentgenogram of a multipara near term, who went into labor following premature spontaneous rupture of the membranes. Rectal examination upon admission to the delivery ward precipitated moderate vaginal bleeding. The placenta was visualized over the anterior wall of the lower uterine segment with its thickest region located by the lower arrow. The upper arrow is directed toward the anterior wall of the fundus, which is of normal thickness. The lumbar region of the fetal spine and the buttocks are flush against the placenta. This location of the placenta (placenta previa) was confirmed at the time of delivery by low cervical cesarean section.

does not in itself affect localization of the placenta by this method, for in only 1 of 6 cases of transverse presentation was the placenta not visualized and then because of hydramnios. Moreover, in each of 22 cases of breech position, the placenta was clearly visualized; the 5 instances of nonvisualization in association with breech positions were due to grossly poor films (3) and hydramnios (2). Except for the above recorded breeches and transverses, the extrauterine pregnancy which was diagnosed roentgenographically, and 2 cases of face presentation, all fetuses pre-

the roentgenograms. Unsatisfactory x-ray films were obtained in 3.05 per cent of the cases, and it was impossible to visualize the placenta in 2 of 8 cases of twin pregnancy. Immaturity, provided the pregnancy has advanced beyond the midpoint, and abnormal presentations and positions are not hindering factors in visualization.

3. Calcification of the placenta is rarely extensive enough to aid in localization of the placental site. No other adjuncts to actual visualization were found. Fetal position is not a reliable criterion of the location of the placenta.

4. No errors in roentgenologic localization of the placenta were found in the 53 instances which were checked by reliable clinical methods.

5. The placental implantations were almost equally divided between anterior and posterior walls of the fundus. However, with low implantation, essentially eight times as many placentas were found implanted on the anterior as on the posterior wall of the lower uterine segment.

6. The average thickness of the walls of the fundus uteri near term measured 1.24 cm. on the roentgenograms which were made at a distance of 42 inches.

7. Only 11 (12 per cent) of 92 cases of vaginal bleeding were found roentgenographically and clinically to have true placenta previa; 15 other cases presented merely x-ray evidence of low implantation of the placenta, without the usual clinical signs.

8. Soft tissue roentgenography in obstetrics finds its greatest usefulness in those cases of vaginal bleeding where the whole of the placenta can be visualized above the level of the iliac crests and these constitute the great majority, 88 per cent, of the instances of vaginal bleeding in the latter months of pregnancy.

We are deeply indebted to Mr. J. C. Fletcher, Chief Technician of the Department of Roentgenology, for his untiring efforts in developing the soft tissue technique in our x-ray laboratory, and for his valuable aid in obtaining photographic reproductions of the roentgenograms; also to Mr. Arthur W. Fuchs of the Medical Division of the Eastman Kodak Company, for expert aid with the photographic reproductions.

REFERENCES

- (1) *Dippel, A. Louis, and Brown, Webster H.*: New England J. Med. 223: 317, 1940.
- (2) *Brown, Webster H., and Dippel, A. Louis*: Bull. Johns Hopkins Hosp. 66: 90, 1940.
- (3) *Snow, William, and Powell, C. B.*: Am. J. Roentgenol. 31: 37, 1934.
- (4) *Smith, R. Manges*: Personal communication.
- (5) *Holland, Eardley*: Lancet 199: 591, 1920.
- (6) *Torpin, Richard*: AM. J. OBST. & GYNEC. 35: 683, 1938.
- (7) *Idem*: J. Obst. & Gynaec. Brit. Emp. 45: 993, 1938.
- (8) *Beck, Alfred C., and Light, Frank P.*: AM. J. OBST. & GYNEC. 35: 1028, 1938.
- (9) *Jablonski, K., and Meisels, E.*: Zentralbl. f. Gynäk. 62: 532, 1938.

visualize the site of the previous incision would be greatly increased by positioning the patient in the true lateral, or in an oblique position, in order to bring this site into the plane parallel to the film.



Fig. 4.—Roentgenogram of a secundipara, whose first delivery was effected by classical cesarean section, on account of fulminating pre-eclampsia. The post-operative course was moderately febrile, but thought to have been due to acute bronchitis. The roentgenogram shows irregular thinning of the anterior uterine wall. The area located by the arrows was found at operation to measure less than 3.0 mm. in thickness. The placenta is located on the posterior wall of the fundus.

CONCLUSIONS

1. The placenta was clearly visualized by soft tissue roentgenography in 236, or 90 per cent, of 262 observations on 259 patients, in 261 pregnancies.
2. The greatest factor interfering with visualization was found to be hydramnios, and accounted for nonvisualization in 5.73 per cent of

Age is an important factor. The proportion of chronic nephritis increases rapidly after thirty-five years. Until then the incidence of the disease is about stationary, regardless of age.

In this series multiparity does not seem to increase the incidence as much as commonly thought. From the fifth pregnancy on, the rate about doubles, but beyond this increasing parity does not cause an increasing incidence.

TABLE I. RATIO OF CHRONIC NEPHRITIS TO OTHER DEATHS

YEAR	TOTAL BIRTHS	TOTAL PUERPERAL DEATHS	NO. OF CHRONIC NEPHRITIS	% OF CHRONIC NEPHRITIS
1931	33,773	248	10	4.0
1932	31,766	239	7	2.9
1933	29,241	152	10	6.5
1934	29,485	164	7	4.2
1935	29,723	156	2	1.2
1936	29,396	174	3	1.7
1937	29,771	117	1	0.8
1938	30,447	99	4	4.0

TABLE II. RATIO OF CHRONIC NEPHRITIS TO OTHER DEATHS BY AGE GROUPS

AGE	15-19	20-24	25-29	30-34	35-39	40-44	NO RECORD
All deaths	52	376	335	281	226	77	2
Chronic nephritis	2	2	10	8	13	8	1
Per cent	3.9	0.5	2.9	2.8	5.7	10.4	
Incidence increases after 35 years.							

TABLE III. RATIO OF PARITY TO CHRONIC NEPHRITIS

PARA	CHRONIC NEPHRITIS	PER CENT	ALL DEATHS
1	9	1.9	474
2	8	4.0	198
3	4	2.8	141
4	1	0.9	106
5	6	7.1	84
6	3	8.5	35
7	2	5.5	36
8	2	4.1	48
9	1	4.1	24
10	3	9.6	31
11	3	21.4	14
12	1	7.7	13
No record	1		145
Totals	44		1,349
Incidence increased from para v upward.			

CLINICAL CHARACTERISTICS

Twenty-five of these patients had a history suggestive of previous toxemia. The most extreme example is that of an 18-year-old para ii who was permanently blinded by toxemia at the birth of her first baby, one and a half years earlier. When she became pregnant again she reported to the prenatal clinic at twenty-six weeks with a blood pressure of 210/140. Unfortunately, the seriousness of the situation was not recognized by the physician on the first visit, and she was admitted to the hospital two weeks later in fatal coma and convulsions.

A less dramatic, but just as significant, history was that of a 43-year-old para viii who gave a history of six or seven miscarriages, refused to consult a physician until she was brought into the hospital, twenty-four weeks pregnant, in convulsions and died six and one-half hours later.

CHRONIC NEPHRITIS AND PREGNANCY FATALITIES IN PHILADELPHIA*

NEWLIN F. PAXSON, B.S., M.D., F.A.C.S., PHILADELPHIA, PA.

THIS study represents part of the work of the Philadelphia Maternal Mortality Committee, under the Chairmanship of Dr. Phillip F. Williams. It consists of an analysis of the fatal cases of chronic nephritis complicated by pregnancy occurring in Philadelphia from Jan. 1, 1931, to Dec. 31, 1938, an eight-year study.

The statistics were analyzed for answers to the following questions:

1. What is the incidence of chronic nephritis in relation to other causes of obstetric death?
2. What are the biologic characteristics of this disease in its fatal form?
3. Were these deaths all unavoidable and, if not
4. What avoidable factors can be controlled by the medical profession?
5. What is the ideal management of a case of chronic nephritis complicated by pregnancy, in the light of our present-day knowledge?

The term chronic nephritis is vague and includes three forms:

1. Chronic glomerulonephritis.
2. Nephrosclerosis.
3. Nephrosis.

There has been no attempt to differentiate these forms. To do so would be impossible from the data available in the hospital and mortality committee records. As will be seen from the detailed analysis, the majority, if not all, were nephrosclerotics; at least, hypertension and vasospasm were present in every case.

The conclusions of the committee were followed in every case even when I disagreed with the assignment of responsibility or diagnosis. Although a group of human beings may occasionally err, in the long run the findings of the Committee will be found accurate.

INCIDENCE

The series is composed of 44 cases. Forty died in hospitals, of which two died while being transported to the hospital (one from New Jersey) and were pronounced dead on arrival. These deaths occurred in 20 of the 26 hospitals in Philadelphia, including all the medical college hospitals. Four died at home.

During the eight-year period, there were 1,349 puerperal deaths, so that the incidence of fatal nephritis is about 3.25 per cent of all deaths.

Table I also shows the decreasing maternal death rate. Chronic nephritis causes only about 3 per cent of all deaths.

It must be remembered that only primary mortality is considered in this paper. Stander has shown that about 40 per cent of nephritics that recover die within the ten-year period following delivery. Thus the problem is greater than the primary death rate would indicate.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.